BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Corrections to the Specification

Applicants have amended the title of the application as requested by the Examiner to describe more clearly the invention as claimed in the instant application. The Specification also has been amended to correct a number of typographical/proofreading errors. For example, the Specification has been amended to correct a typographical/proofreading error for the Uemura et al. reference cited on page 3, line 28.

The Specification has also been amended to correct typographical/ proofreading errors in Table 1. On page 26, line 4, "acceptor" has been deleted and "donor" has been inserted therefore. That is a correction of an obvious error. At page 25, lines 18-20, the Specification reads, "Table 1 below lists the splice donor and acceptor sequences that conform to consensus splice sequences including the AG-GT motif. . . .", but the headings of Table 1 only refer to "5'splice acceptor" and "3' splice acceptor" sequences. The upper half of Table 1 lists the 11 exons of the human MN gene, and the heading refers to "5' splice" sequences. As a 5' splice site would be a donor site, the heading in line 4 of Table 1 should obviously read "5' splice donor".

The correction at page 26, line 14 of Table 1 changes the Genomic Position of Exon 10 from "10350-70431" to "10350-10431". That error is obvious in that SEQ ID NO.: 37 contains 82 base pairs, and further in view of the context of Exon 10, for example, in light of Intron 10's genomic position, which begins at nucleotide 10432 [as shown in the last line of Table 1, supra].

The Specification has also been corrected as requested by the Examiner to conform to the trademark usage policy set forth in section 5 of the Office Action. At page 44, line 16, the same generic description for the "ONE Hybrid System®" has been inserted as can be found for that trademarked product at page 48, line 33 to page 49, line 1 of the Specification. Trademark designations have also been added as requested by the Examiner at page 57, lines 15 and 17, at page 58, line 12, and at page 74, line 5.

Corrections to SEQUENCE LISTING

The sequence for SEQ ID NO: 76 was given incorrectly in the SEQUENCE LISTING as atacagggga t. This incorrect sequence is an obvious typographical error; as seen in Table 1 on page 26 of the description, the correct sequence for SEQ ID NO: 76 (the 5' splice donor for Exon 10) is cacaggtatt a. The sequence atacagggga t is actually the correct sequence for SEQ ID NO: 77 (the 3' splice acceptor for Intron 1), as shown in Table 1 and SEQ ID NO: 77 in the SEQUENCE LISTING. The Applicants are herewith providing a substitute paper copy of the SEQUENCE LISTING and substitute computer readable copy (CRF), and request that the SEQ ID NO: 76 in the SEQUENCE LISTING be amended to read cacaggtatt a to be consistent with the specification. The SEQUENCE LISTING information recorded in computer readable form is identical to the written paper copy.

Amendments to the Claims

Independent Claims 22, 30 and 42 have been amended to specify that the claimed anti-idiotype antibody is to an "idiotype of a second antibody, wherein said idiotype of said second antibody specifically binds to an epitope of an MN protein", to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. Claims 23 and 31 have been amended to be consistent with the independent claims (Claims 22 and 30) from which they depend.

Applicants respectfully submit that those amendments are made to clarify the meaning of MN-specific anti-idiotype antibodies, and respectfully but emphatically emphasize that those amendments are supported by what was conventionally known in the art about anti-idiotype antibodies as of the earliest priority date for the subject invention. Applicants at least can be shown to have possession of the instantly claimed invention at the Oct. 21, 1992 filing date of the earliest U.S. priority application [U.S. Serial No. 07/964,589] which was issued on Feb. 7, 1995 as U.S. Patent No. 5,387,676 ["the '676 patent"]. The Zavada et al. '676 patent states at least at column 25, lines 1-3: "It will further be appreciated that anti-idiotype antibodies to antibodies to MN proteins/polypeptides are also useful as vaccines and can be similarly formulated." Applicants respectfully point out that in view of the disclosure of the '676 patent [which

provides the MN cDNA sequence and deduced amino acid sequence, which were corrected by Declarations of the inventors (Zavada et al.) in view of the ATCC deposit of the VU-M75 hybridoma; please see Appendix E for the corrected amino acid and cDNA sequences], and in view of what was conventionally known in the art at the priority date of the patent, one of skill in the art would know how to make and use the instantly claimed MN-specific anti-idiotype antibodies.

One of skill in the art would see that inherent in the statement at column 25, lines 1-3 of the Zavada et al. '676 patent is the necessity that the anti-idiotype antibodies to antibodies to MN proteins/polypeptides must mimic MN proteins/polypeptides to be useful, as MN protein/polypeptides would be, when formulated in a vaccine. Applicants respectfully point out that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

Explicitly detailed support for the amendments to independent Claims 22, 30 and 42 and dependent Claims 23 and 31can be found in the instant specification at least at page 12, line 29 to page 13, line 2; at page 13, lines 16-17 and lines 27-31; at page 15, lines 24-33; at page 75, line 11 to page 76, line 21; and at page 81, lines 27-32. It is clear throughout the specification that the type of anti-idiotype antibody that is being claimed is "MN-specific". For example, the specification at page 75, lines 14-15 states: "**MN-specific anti-idiotype** antibodies have therapeutic utility as a vaccine for neoplastic disease associated with abnormal MN expression." [Emphasis added.] As discussed above in regard to the '676 patent, one of skill in the art could only interpret such MN-specific anti-idiotype antibodies as being directed to an idiotype that specifically binds to an MN protein/polypeptide epitope.

The specification defines anti-idiotype antibodies that mimic corresponding normal antigens at page 75, lines 20-25:

> Uemura et al. . . . define an anti-idiotype antibody (Ab2) as "an antibody directed against an antigenic determinant located within a variable region of the immunoglobulin

> molecule. Ab2 mimicking the normal antigen (so-called internal image Ab2) may be used as a surrogate antigen for vaccination to trigger the host's immune system specifically against the nominal antigen."

[Emphasis added.] Additional particular support for "internal image" anti-idiotype antibodies can be found at page 81, lines 29-30, which reads: "[A]nti-idiotype antibodies to MN-specific antibodies mimic MN protein/polypeptide."

Independent Claims 22, 30 and 42 have also been amended to specify the stringent hybridization conditions of "50% formamide at 42 degrees C", for purposes of increased clarity and particularity. Dependent Claim 52, which previously specified the stringent hybridization conditions of "50% formamide at 42 degrees C", has been cancelled as redundant. The stringent hybridization conditions of "50% formamide at 42 degrees C" are set forth in the instant specification at least at page 7, lines 16-18 and at page 8, line 13, and stringent hybridization conditions are discussed at page 60, lines 12-19. Those specific hybridization conditions can also be found in Example 12 of the Zavada et al. '676 patent [that is, in the earliest U.S. priority application for the subject invention, U.S. Serial No. 07/964,589 filed Oct. 21, 1992, now U.S. Patent No. 5,387,676 (issued Feb. 7, 1995); "the '676 patent"].

Claims 37, 47 and 48 have been amended to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention. Claim 37 has been amended to be consistent with independent Claim 30 from which it depends in using the phrase "nucleic acid comprises a polynucleotide containing at least," and further to be consistent with Claims 36 and 38 in using the phrase "a polynucleotide containing at least. . . ." In Claims 47 and 48, the phrase "MN polypeptide is encoded by a fragment of" has been replaced by the phrase "nucleic acid has a nucleotide sequence from", for purposes of increased clarity and particularity.

Applicants respectfully conclude that no new matter has been entered by the above amendments. Claims 22, 23, 30, 31, 36-38, 42, 43 and 46-48 are now pending and under examination. Applicants respectfully request entry of the above amendments and reconsideration of the claims as amended.

Title (Section 4 of Office Action)

As requested by the Examiner and noted above, the title of the application has been changed to be more "clearly indicative of the invention to which the claims are directed." [Office Action, Section 4, page 2.]

Trademark Usage (Section 5 of Office Action)

Applicants respectfully submit that the instant specification's references to trademarked products now conform to the usage policy set forth in section 5 of the Office Action in view of the amendments to the Specification at page 44, line 16, at page 57, lines 15 and 17, at page 58, line 12 and at page 74, line 5.

35 U.S.C. Section 112, Second Paragraph Rejection (Sections 6-7 of Office Action)

Claims 22, 23, 30, 31, 36-38, 42, 43 and 46-48 stand rejected under 35 U.S.C. Section 112, second paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." [Office Action, Section 7, page 3.] Applicants respectfully traverse and request that the Examiner reconsider and withdraw the rejection in view of the amendments to claims 22, 23, 30, 31, 37, 42, 47 and 48 and the following remarks.

Subsection 7a.

At page 3, Section 7a the Office Action states:

> Claims 22-23, 30-31, 36-38, 42-43 and 46-48 are indefinite for reciting 'hybridize under stringent conditions' in claim 22, 30 and 42 because the exact meaning of the phrase is not clear. . . . The specification discloses several conditions on page 60 as well as 'less stringent' and 'more stringent' and it is not clear which if any of these conditions are required for the claims.

Applicants respectfully point out that the amendments to independent claims 22, 30 and 42 address that objection by reciting the specific stringent hybridization conditions "of 50% formamide at 42 degrees C". As indicated above, the stringent hybridization conditions of "50% formamide at 42 degrees C" are found in Example 12 of the earliest U.S. priority application [now U.S. Patent No. 5,387,676 ("the '676 patent")] and are set

forth at page 7, lines 16-18 and page 8, lines 12-18. For example, the specification states at page 7, lines 16-17: "nucleotide (nt) sequences that hybridize specifically under stringent conditions, for example, of 50% formamide at 42°C." [Emphasis added.]

In view of the above remarks and the clarifying amendments to Claims 22, 30 and 42, Applicants respectfully submit that the pending claims have been shown not to be indefinite.

Subsection 7b.

At page 3, Section 7b the Office Action states: "Claim 37 recites the limitation 'said polynucleotide'. There is insufficient antecedent basis for this limitation in the claim. It is unclear which polynucleotide recited in the parent claim (claim 30) is required by dependent Claim 37." Applicants respectfully submit that the amendment to Claim 37 which reads wherein "said nucleic acid comprises a polynucleotide" clarifies and specifies the subject "polynucleotide" and renders Claim 37 consistent with Claim 30 in antecedent basis and structure. Further, Claim 37 as amended is analogously worded to Claims 36 and 38 in regard to the phrase "wherein said nucleic acid comprises a polynucleotide containing. . . ."

Subsection 7c.

The Office Action in section 7c at page 3 states that "Claims 47-48 are indefinite for reciting 'fragment of SEQ ID NO:1'." Applicants respectfully point out that the amendments to claims 47 and 48 address that rejection. Claims 47 and 48 have been amended for increased clarity and particularity to read: "said nucleic acid has a nucleotide sequence from SEQ ID NO: 1", rather than "said MN polypeptide is encoded by a fragment of SEQ ID NO: 1". Applicants respectfully submit that that alternative wording of claims 47 and 48 by removing the term "fragment" considered by the Examiner to be ambiguous in the context of the dependent claims addresses the subject rejection.

Applicants respectfully conclude that the pending claims as amended for particularity and clarity comply with the requirements of 35 U.S.C. § 112, second

paragraph, and respectfully request that the Examiner reconsider and withdraw the instant rejection in view of the above remarks.

35 U.S.C. Section 112, First Paragraph Rejection (Sections 8-9 of Office Action)

Claims 30, 31, 36-38, 42, 43, 46-48 and 52 (now cancelled) stand rejected under 35 U.S.C. 112, first paragraph, because the claims contain

> subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.
>
> . . . .
>
> The preliminary amendment filed 9/27/2001 pointed to the specification where support can be found for the newly added claims, however, support for the instant claim limitations can not apparently be found. Support for claims reciting an anti-idiotype antibody that binds to an antibody that specifically binds to an MN polypeptide that is encoded by a polynucleotide that comprises a certain number of nucleotides of SEQ ID NO: 1 is not supported by the disclosure pointed to by applicant on **pages 8-9** and at **page 60** because the disclosure on these pages only provides support for nucleic acid probes comprising "a polynucleotide containing different numbers of nucleotides." Although the polynucleotides are disclosed as encoding MN proteins or polypeptides there is apparently no support for an antibody that binds said MN proteins or polypeptides, much less an anti-idiotype antibody to the antibody, which binds said MN proteins or polypeptides. Additionally, there is no apparent support for claims 46-49, which recite the broad limitation of an anti-idiotype antibody to an antibody that binds an MN protein or polypeptide wherein the MN protein or polypeptide is encoded by any fragment of SEQ ID NO: 1.

[Office Action, Section 9, pages 4-5; emphasis added.] Applicants first respectfully traverse this rejection, pointing out that there is apparently a misunderstanding, in that the passages cited by the Examiner in the Office Action are not the passages that Applicants cited in the Preliminary Amendment of September 27, 2001 as support for claims reciting MN-specific anti-idiotype antibody. Applicants are submitting herewith a

copy of page 65 from that Preliminary Amendment (Appendix A) with the support for anti-idiotype antibodies highlighted, wherein Applicants stated:

> Support in the Specification concerning anti-idiotype antibodies to MN-specific antibodies and anti-anti-idiotype antibodies to such anti-idiotype antibodies can be found at least at page 12, line 29 to page 13, line 31; at page 15, lines 24-33; at page 75, line 11 to page 76, line 21; at page 81, lines 27-32; and at page 122, lines 9-12.

For example, one entire section of the specification, at page 75, line 11 to page 76, line 21, is entitled Anti-Idiotype MN-Specific Antibodies as Tumor Vaccines and Anti-Anti-Idiotype Antibody Sera as Immunotherapeutic. In other passages cited above as support for the new claims, the instant specification states:

> Still further, such therapeutic/prophylactic methods comprise inducing MN-specific antibody production within a patient by injecting said patient with an anti-idiotype antibody to a MN-specific antibody. Still further, such therapeutic methods can include treating a patient with a preneoplastic and/or neoplastic disease characterized by abnormal MN expression by administering to said patient a therapeutically effective amount of an anti-anti-idiotype MN-specific antibody serum, alone or in combination with one or more cytokines, preferably with IFN and/or IL-2.

[Instant Specification, page 12, line 29 to page 13, line 2; emphasis added.]

> Also disclosed are anti-idiotype antibodies to MN-specific antibodies, and anti-anti-idiotype antibodies thereto, polyclonal or monoclonal. Such anti-idiotype antibodies are useful as vaccines, and the anti-anti-idiotype antibody sera are therapeutically useful against neoplastic diseases associated with abnormal MN expression.

[Instant Specification, page 13, lines 27-31; emphasis added.]

Applicants further respectfully traverse this rejection pointing out that the claims as amended in the Preliminary Amendment Express Mailed to the PTO on September 27, 2001 only amended the claims to define with particularity and clarity the meaning of the terms "MN protein" and "MN polypeptide," and that said terms are well supported in the earliest U.S. priority application for the instantly claimed invention, that is, in U.S. Serial No. 07/964,589, filed October 21, 1992, which was issued on February

7, 1995 as Zavada et al., U.S. Patent No. 5,387,676 ("the '676 patent"), as well as in the instant application at page 53, lines 7-10.

That Zavada et al. '676 patent, as mentioned above, provides support for the claimed invention at least at column 25, lines 1-3 which states: "It will further be appreciated that anti-idiotype antibodies to antibodies to **MN proteins/polypeptides** are also useful as vaccines and can be similarly formulated." [Emphasis added.] Further as indicated above, patent case law makes it clear that "A patent need not teach, and preferably omits, what is well known in the art." [Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987); emphasis added.]

The Office Action itself points out that it was well known in the art at the time of the earliest priority date for the subject invention how to make and use anti-idiotype antibodies once an immunogenic protein/polypeptide has been identified. The Office Action states at page 8:

> The art teaches that the process of generating internal image anti-idiotype antibodies are well known to those of skill in the art and can result in the production of internal image antibodies that mimic the immunological properties of the initial antigen (i.e., tumor antigen or infectious agent). For support, See Raychaudhuri S., U.S. Patent 5,270,202, bridging paragraph of columns 2-3).

The cited Raychaudhuri, S. '202 patent was filed on March 12, 1991, and a number of references cited in the '202 patent (particularly in the paragraph bridging columns 2-3) provide evidence of the conventionality in the art of making and using anti-idiotype antibodies well before the earliest priority date for the instantly claimed MN-specific anti-idiotype antibodies.

The Zavada et al. '676 patent at column 13, lines 53-68 defines the phrase "MN proteins and/or polypeptides" (MN proteins/polypeptides)

> [t]o mean proteins and/or polypeptides encoded by an MN gene or fragments thereof. An exemplary and preferred MN protein is that for which the predicted amino acid sequence is shown in FIG. 1A-1B. Preferred MN proteins/polypeptides are those proteins and/or polypeptides that have substantial homology with that MN protein shown in FIG. 1A-1B.

> A "polypeptide" is a chain of amino acids covalently bound by peptide linkages and is herein considered to be composed of 50 or less amino acids. A "protein" is herein defined to be a polypeptide composed of more than 50 amino acids.

Antibodies to MN protein/polypeptides are understood to be antibodies to proteins/polypeptides a shown in Figure 1A-1B (corrected; please see Appendix E) and substantially homologous proteins and/or polypeptides. Substantially homologous MN proteins/polypeptides are considered to be those that are encoded by nucleotide sequences that hybridize to the MN cDNA of SEQ ID NO: 1 of the '676 patent under stringent hybridization conditions.

Claim 22 was amended in the September 27, 2001 Preliminary Amendment to incorporate the language used in claim 1 of the '676 patent to define the term "MN protein." Claim 1 of the '676 patent reads:

> 1. An isolated nucleic acid encoding a MN protein wherein the nucleotide sequence for said nucleic acid is selected from the group consisting of:
>
> (a) SEQ. ID. NO.: 1;
>
> (b) nucleotide sequences that hybridize under stringent conditions to SEQ. ID. NO.: 1 or to its complementary strand; and
>
> (c) nucleotide sequences that differ from SEQ. ID. NO.: 1 and from the nucleotide sequences of (b) in codon sequence due to the degeneracy of the genetic code.

Applicants respectfully conclude that the amendment to Claim 22 from the Preliminary Amendment is well supported in the earliest U.S. priority application for the subject invention, that is, by the Zavada et al. '676 patent filed on Oct. 21, 1992.

The instant application repeats essentially that same language throughout its Specification. For example, the Specification at page 7, lines 12-21 describes

> isolated nucleic acid sequences **that encode MN proteins or polypeptides** wherein the nucleotide sequences for said nucleic acids are selected from the group consisting of:
>
> (a) SEQ ID NO: 1;

> **(b) nucleotide (nt) sequences that hybridize specifically under stringent conditions, for example, of 50% formamide at 42°C, to SEQ ID NO: 1 or to its complement;**
>
> (c) nucleotide sequences that differ from SEQ ID NO: 1 or from the nucleotide sequences of (b) in codon sequence because of the degeneracy of the genetic code.

[Emphasis added.]

Applicants respectfully conclude that the amendment to Claim 22 of the Preliminary Amendment is well supported in the earliest U.S. priority application, that is, by the '676 patent, and in the instant application. Claim 23 is dependent on Claim 22, and only changed the phrase "MN-specific antibody" to "antibody that is specific for said MN protein," and is similarly supported by the '676 patent and the instant application.

Independent Claim 30 presented in the Preliminary Amendment is only different from Claim 22 as amended by the Preliminary Amendment in that the antibody binds to "an MN polypeptide" instead of "an MN protein," and said encoding "nucleic acid . . . comprises a polynucleotide containing at least 29 nucleotides. . . ." As indicated above, the '676 patent refers to MN polypeptides composed of 50 or less amino acids, whereas MN proteins are composed of more than 50 amino acids. [Zavada et al. '676 patent, column 13, lines 64-68.] The '676 patent at column 3, lines 59-61 states: "MN proteins/polypeptides of this invention are serologically active, immunogenic and/or antigenic." One of skill in the art would recognize that the size of the MN polypeptide is only limited by its immunogenicity, and that Claim 30 requires that it be encoded by a polynucleotide containing at least 29 nucleotides and that the claimed anti-idiotype antibody is directed to an antibody that specifically binds to said MN polypeptide.

The instant specification states at least at page 10, lines 15-24:

> Recombinant nucleic acids that encode MN fusion proteins are claimed as comprising an MN protein or MN polypeptide and a non-MN protein or polypeptide wherein the nucleotide sequence for the **portion of the nucleic acid encoding the MN protein or polypeptide is selected from the group consisting of**:

(a) SEQ ID NO: 1;

(b) nucleotide sequences that hybridize under stringent conditions to SEQ ID NO: 1 or to its complement; and

(c) degenerate variants of SEQ ID NO: 1, and of the nucleotide sequences of (b); **wherein the nucleic acid encoding said MN protein or polypeptide preferably contains at least twenty-five nts**.

[Emphasis added.]

The instant application also states at page 8, lines 1-7:

> Further, this invention concerns nucleic acid probes which are **fragments of the isolated nucleic acids that encode MN proteins or polypeptides** and/or are from the MN genomic sequence which meet the above hybridization criteria [stringent, as, for example, 50% formamide at 42°C]. Preferably said nucleic acid probes are comprised of at least 25 nts, more preferably at least 27 nts, still more preferably at least 29 nts, further preferably at least 50 nts, further more preferably at least 100 nts, and even more preferably at least 150 nts.

[Emphasis added.] Applicants respectfully submit that the phrases in Claims 30, 36, 37, 38, 42, and 43 referring to "an MN polypeptide encoded by a nucleic acid that comprises a polynucleotide containing at least . . ." 25, 27, 29, 50, 100 or 150 nucleotides are supported in the instant application specifically, and in general in the '676 patent.

Applicants respectfully submit that ones of skill in the art realize that a fragment of cDNA encoding an immunogenic polypeptide only has to encode a sufficient number of amino acids to comprise an epitope, probably a linear epitope of just a few amino acids. A fragment of an encoding cDNA sequence is still an encoding cDNA sequence. A cDNA sequence of 25 nucleotides would likely encode about 8 amino acids, which number are sufficient to encompass a linear epitope. As shown above, it is conventional in the art to prepare antibodies against such immunogenic polypeptides containing an epitope.

The Office Action states at page 5 that "there is apparently no support for an antibody that binds said MN proteins or polypeptides, much less an anti-idiotype

antibody to the antibody, which binds said MN proteins or polypeptides." Applicants respectfully but most forcefully disagree, pointing out first that the '676 patent as the earliest U.S. priority application, more than amply and clearly supports antibodies to MN protein/polypeptides and MN-specific anti-idiotype antibodies. For example, the '676 patent states at column 3, line 59 to column 4, line 22 reads:

> MN protein/polypeptides of this invention are serologically active, immunogenic and/or antigenic. They can further be used as immunogens to produce MN-specific antibodies, polyclonal and/or monoclonal, as well as an immune T-cell response.
>
> The invention further is directed to MN-specific antibodies, which can be used diagnostically/prognostically and may be used therapeutically. . . . Still further, such antibodies can be used to affinity purify MN proteins and polypeptides.

The instant application, for example, at page 12, lines 12-14, refers to preferred MN-specific antibodies for therapeutic use that have "an epitope selected from the group consisting of SEQ ID NOS: 10 and 98-103." Those SEQ ID NOS refer to particular epitopes from 4 amino acids [SEQ ID NO: 99 (EEDL)] to 7 amino acids [SEQ ID NO: 102 (EEDLPSE)] as shown at least at pages 11, 12, 13, 14, 72, 118 and 119 of the instant specification.

Applicants respectfully conclude that as shown in detail above, the pending claims are well supported by the earliest U.S. priority application, that is, the by the '676 patent filed on October 21, 1992, and by the instant application. Further, Applicants respectfully but emphatically repeat basic tenets of patent law that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

35 U.S.C. Section 112, First Paragraph Rejection (Section 10 of Office Action)

Claims 22, 30, 36-38, 42, 43 and 46-48 stand rejected under 35 U.S.C. Section 112, first paragraph, because:

> the specification, while being enabling for a anti-idiotype antibody type beta ($Ab_2\beta$ . . .) to monoclonal antibodies . . . that specifically bind SEQ ID NO: 2 . . . , does not reasonably provide enablement for just any anti-idiotypic (i.e., -alpha ($Ab_2\alpha$) or –epsilon ($Ab_2\epsilon$)) antibody that binds just any antibody that binds to an MN protein encoded by SEQ ID NO:1 or just any fragment of SEQ ID NO:1 that does not encode an epitope recognized by Mabs M75, MN9, MN12, MN7 and G250 or an MN protein/polypeptide encoded by polynucleotides that hybridize under stringent conditions to the complement of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

[Office Action, page 6, Section 10.] Applicants respectfully traverse this rejection, arguing first, that the amendments to the subject claims address the instant rejection with respect to the scope of the claimed anti-idiotype antibodies to MN-specific antibodies, as explained in detail below; second, that the pioneering nature of the instant invention entitles the Applicants to broad claim coverage with respect to the scope of MN protein/polypeptide encoded by polynucleotides that hybridize under specific stringent conditions to the complement of SEQ ID NO: 1; and third, that the claims as amended for particularity and clarity provide a reasonable scope commensurate with enablement.

I. Enablement for "Anti-idiotypic Antibody"

Applicants respectfully point out that independent vlaims 22, 30 and 42 have now been amended to indicate that the claimed anti-idiotype antibody is not "any anti-idiotypic antibody that binds any antibody that binds an MN protein", but one that specifically binds to an "idiotype of a second antibody, wherein said idiotype of said second antibody specifically binds an epitope of MN protein." [Emphasis added.] It is clear that claim 22 and analogous claims 30 and 42 as amended now refer only to an

anti-idiotype antibody of the beta type ($Ab_2\beta$) to monoclonal antibodies that specifically bind the MN protein or fragments thereof, and do not encompass "any anti-idiotypic antibody" that binds "just any antibody" that binds to an "MN protein encoded by SEQ ID NO: 1. . . ."

As the Examiner states at page 8 of the Office Action: "The art teaches that the process of generating internal image anti-idiotype antibodies are well known to those of skill in the art and can result in the production of internal image antibodies that mimic the immunological properties of the initial antigen (i.e., tumor antigen or infectious agent)." Therefore, the subject claims as amended are enabled for anti-idiotype antibodies mimicking the MN antigen.

Enablement for Anti-idiotypic Antibody to an Idiotype of a Second Antibody that Specifically Binds to an Epitope of an MN Protein or of a MN Polypeptide Encoded by SEQ ID NO:1 or a Fragment of SEQ ID NO:1

As in the above comments, Applicants respectfully point out that independent Claims 22, 30 and 42 have now been amended to indicate that the claimed anti-idiotype antibody specifically binds to an "**idiotype of a second antibody, wherein said idiotype of said second antibody specifically binds to an epitope of an MN protein**." [Emphasis added.] As amended, Claims 22, 30 and 42 clearly refer only to an anti-idiotype antibody to an antibody that specifically binds an epitope of the MN protein or of an MN polypeptide, and do not "encompass anti-idiotypic antibodies that bind to any antibody that binds anywhere on an MN protein encoded by SEQ ID NO:1. . . ." [Office Action, section 10, page 8; emphasis added.]

Therefore, the subject claims as amended are enabled for anti-idiotype antibodies with binding sites resembling the epitopes of the MN antigen encoded by SEQ ID NO: 1.

Enablement for Selecting MN Proteins and MN Polynucleotides Encoded by Nucleic Acids that Hybridize under Specified Stringent Hybridization Conditions to SEQ ID NO: 1 [MN Full-Length cDNA (1522 base pairs) Shown in Figure 1] that are 80-90% Homologous to SEQ ID NO: 1

The Office Action further states in Section 10, at page 9:

> The claims are broad because they do not require that the claimed polynucleotides and the encoded polypeptides to be identical to the disclosed MN sequences (i.e., SEQ ID Nos. 1 and 2) and because the claims have no functional limitation. The claims also encompass polynucleotides and polynucleotide fragments that hybridize to the complement of SEQ ID NO: 1 under stringent conditions, however, the claims do not recite under what full set of conditions are used for hybridization or if the polynucleotides hybridize to the full-length of SEQ ID NO: 1 or if the hybridized polynucleotides encode a polypeptide of SEQ ID NO: 2 (i.e., the disclosed MN polypeptide). Even if the claimed polynucleotides and polypeptides encoded thereby had a function the specification does not provide guidance for using polynucleotides related to (see page 52), but not identical to SEQ ID NO:1 or polypeptides related to, but not identical to the polypeptide of SEQ ID NO: 2.

[Emphasis added.]

Applicants respectfully point out that independent Claims 22, 30 and 42 have been amended to specify the stringent hybridization conditions "of 50% formamide at 42 degrees C," and therefore the "polynucleotides that hybridize under stringent hybridization conditions to SEQ ID NO: 1's complement" are defined in compliance with the written description requirement of 35 U.S.C. Section 112, first paragraph. Applicants respectfully submit that if the "stringent hybridization conditions" for hybridizing to the complement are defined, "polynucleotides that hybridize to the complement of SEQ ID NO: 1" are also defined. Further, the specification states at page 52, lines 16-17: "Only very closely related nt sequences having a homology of at least 80-90% would hybridize to each other under stringent conditions." [Emphasis added.] That statement provides structural characterization of "polynucleotides that hybridize under stringent conditions to SEQ ID NO: 1's complement."

Applicants respectfully point out that the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1, "Written Description" Requirement [hereinafter cited as "Guidelines"]; Fed. Register, 66(4) (January 5, 2001) at page 1105, column 1] note under the sub-heading "A. Original Claims":

> There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. . . . However, the issue of lack of

> adequate written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention. . . . The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. . . .

[Emphasis added.] The Guidelines [id. at page 1106, column 1] indicate that "the description need only describe in detail that which is new or not conventional." [Emphasis added.]

The Court of Customs and Patent Appeals (CCPA), predecessor court to the Federal Circuit, stated in In re Goffe, 191 USPQ 429 at 431 (CCPA 1976):

> [To] provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work . . . would not serve the constitutional purpose of promoting progress in the useful arts.

The nucleic acid sequence of SEQ ID NO: 1 should be sufficiently descriptive of both its complement and for nucleotides which hybridize to its complement under stringent conditions, that is, that are 80-90% homologous to it, for the written description and enablement requirements of 35 USC 112, first paragraph.

Concerning the use of functional limitation of MN polynucleotides and MN proteins in the claims, Applicants respectfully direct the Examiner's attention to the following relevant paragraphs from the Specification at page 30, lines 10-29:

> Figure 1A-C provides the nucleotide sequence for a full-length MN cDNA clone isolated as described below [SEQ ID NO: 1]. Figure 2A-F provides a complete MN genomic sequence [SEQ ID NO: 5]. Figure 6 shows the nucleotide sequence for a proposed MN promoter [SEQ ID NO: 27].
>
> It is understood that because of the degeneracy of the genetic code, that is, that more than one codon will code for one amino acid [for example, the codons TTA, TTG, CTT, CTC, CTA and CTG each code for the amino acid leucine (leu)], that variations of the nucleotide sequences in, for example, SEQ ID NOS: 1 and 5 wherein one codon is

> substituted for another, would produce a substantially equivalent protein or polypeptide according to this invention. All such variations in the nucleotide sequences of the MN cDNA and complementary nucleic acid sequences are included within the scope of this invention.
>
> It is further understood that the nucleotide sequences herein described and shown in Figures 1, 2 and 6, represent only the precise structures of the cDNA, genomic and promoter nucleotide sequences isolated and described herein. It is expected that slightly modified nucleotide sequences will be found or can be modified by techniques known in the art to code for substantially similar or homologous MN proteins and polypeptides, for example, those having similar epitopes, and such nucleotide sequences and proteins/polypeptides are considered to be equivalents for the purpose of this invention.

[Emphasis added.] Applicants respectfully point out that the above-quoted paragraphs describe MN proteins and MN polynucleotides, as those exemplified by SEQ ID NO: 1 (the full-length MN cDNA of 1522 base pairs from which the amino acid sequence SEQ ID NO: 2 is deduced), and by open reading frames related thereto as indicated; and MN proteins and MN polypeptides, as those substantially similar or homologous to amino acid sequence SEQ ID NO: 2, for example, those having similar epitopes.

Applicant submits that epitopes, for example those represented by SEQ ID NOS: 10-16, have been set forth in the Specification. Two hybridomas that secrete representative MAbs – M75 and MN12 – have been deposited at the ATCC, and their epitopes have been identified as SEQ ID NOS: 10 and 11, respectively. The deposited MAbs M75 and MN12 allow one of skill in the art to identify and isolate MN antigen and can be used in conventional screens to identify MN proteins/polypeptides.

Further regarding the identification of epitopes, conventional screening protocols can be used to determine if a protein or polypeptide encoded by a nt sequence of 29 or more nts that hybridizes to SEQ ID NO. 1 under standard stringent hybridization conditions, as exemplified by 50% formamide at 42 degrees C has epitopes recognized by antibodies that bind specifically to known MN protein/polypeptide, as that having the amino acid sequence of SEQ ID NO: 2 or other naturally occurring MN protein/polypeptide, for example, that expressed on the surface

of HeLa cells that react with MAb 75. The serological activity, the immunogenicity, and the antigenicity of such proteins/polypeptides to fall within the scope of MN proteins/polypeptides need not be to the same extent as the MN protein having the amino acid sequence of SEQ ID NO: 2. Such protein/polypeptide only needs to have some degree of serological activity, immunogenicity and/or antigenicity as displayed by MN proteins/polypeptides. [In re Gardner, 177 USPQ 396, 398 (CCPA 1973.)

Further, one of skill in the art could use a commercially available computer program such as PCGENE™ (IntelliGenetics, Inc., Mountain View, CA) to identify MN epitopes when given SEQ ID NO: 2. Further, there is a section in the Specification entitled "Epitope Mapping" at page 74 that describes the use of a commercially available kit – Novatope® system from Novagen, Inc. – useful for epitope mapping. Still further incorporated by reference is Li et al., Nature, 363: 85-88 (6 May 1993), which provides an analogous example to determine antigenic regions of a protein from cDNA. [Specification, page 74, lines 6-7]. Applicants respectfully submit that such determinations of antigenic sites are well within the conventional skill of the art.

Still further, characteristics of MN proteins/polypeptides are provided throughout the Specification. For example, at page 53, lines 11-16, the Specification indicates:

> MN proteins exhibit several interesting features: cell membrane localization, cell density dependent expression in HeLa cells, correlation with the tumorigenic phenotype of HeLa x fibroblast somatic cell hybrids. . . . MN protein can be found directly in tumor tissue sections but not in general in counterpart normal tissues. . . .

Applicants conclude that the terms MN polynucleotides and MN polypeptides are clear to ones of skill in the art in the context of the instant application, and that the Specification provides enablement for the selection of polynucleotides that hybridize to the complement of SEQ ID NO: 1 under stringent hybridization conditions, that is, that are 80-90% homologous to SEQ ID NO: 1.

Burden of Proof Not Met

At page 7 of the Office Action, the Examiner states: "The specification does not disclose any working examples of an anti-idiotype antibody to an antibody that binds an MN protein. . . ." Further, in the passage bridging pages 8 and 9 of the Office Action, the Examiner refers to Raychaudhuri (U.S. Patent 5,270,202) as teaching that "the successful production of anti-idiotypic antibodies is an unpredictable endeavor (see column 3, lines 44-58)", and to Chatterjee et al. (U.S. Patent 6,235,280 B1) as teaching that "not all anti-idiotype antibodies can be used in therapeutic regimens against tumors. . . . [A]nti-idiotype therapy with respect to tumor origin and antigens expressed should be evaluated on a case-by-case basis since different cancers have widely varying molecular and clinical characteristics (see column 2, lines 39-53)." At page 10 of the Office Action, the Examiner further state: "One of skill in the art would neither expect nor predict the appropriate functioning of the anti-idiotypic antibodies as broadly as claimed."

Applicants respectfully argue that the PTO's initial burden of proof to challenge the presumptively enabling disclosure of the subject application has not been met concerning the claimed anti-idiotype antibody to an antibody that binds to an MN protein or an MN polypeptide, particularly in view of the amendments to the claims and the above arguments. Therefore, Applicants respectfully submit that they need not provide rebuttal evidence.

MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); emphasis in the original.]

The Court of Customs and Patent Appeals (CCPA) reversed a § 112, first paragraph rejection centering on the how-to-use requirement in In re Gardner, 177 USPQ 396, 398 (CCPA 1973). In that case the CCPA pointed out:

> [T]he only matter to be determined is the reasonableness of the Patent Office's doubts. The standard to be applied . . . is ---the absence of utility. . . . [T]here is no requirement in § 112 that all of the claimed compounds have the same degree of utility. Some antihypertensive activity coupled with knowledge as to employment of this activity is all that is necessary to satisfy the how-to-use requirement.

[Id; emphasis in the original.] According to In re Gardner, absence of utility is the standard to apply in determining the reasonableness of the PTO's doubts as to compliance with the how-to-use requirement of § 112. It is not commercial, marketable, or optimal utility that is the standard, but the absence of utility. An invention may be constructively reduced to practice by filing an application with no working examples at all or with paper examples.

The Federal Circuit has stated:

> The first paragraph of § 112 requires nothing more than objective enablement. In re Marzocchi . . . 169 USPQ 367, 369 (CCPA 1971). How such a teaching is set forth either by the use of illustrative examples or by broad terminology, is irrelevant.

[In re Vaeck, 20 USPQ2d 1438 at 1445 (Fed. Cir. 1991).]

Applicants respectfully submit that there is no reason to doubt "the objective truth of statements" relied upon for enabling support for the claimed invention. Applicants respectfully consider MN proteins and MN polypeptides to be uniquely excellent molecules for the development of anti-idiotypic antibodies for use in treating or immunizing one against pre-neoplastic/neoplastic diseases:

(a) MN protein is expressed on the surface of preneoplastic/neoplastic cells and is accessible to MN-specific antibodies;

(b) MN protein is expressed in a high percentage of human tumors; and

(c) MN protein is rarely expressed in normal cells, except for in normal cells of the stomach mucosa.

For the reasons detailed above, Applicants respectfully conclude that the PTO's burden to provide "reason to doubt the objective truth of the statements contained" in the instant specification "which must be relied upon for enabling support"

for the claimed invention has not been met. [In re Marzocchi, supra.] Applicants respectfully conclude that there is no reason to doubt that the Specification is enabling for the claimed anti-idiotypic antibodies that mimic MN proteins/polypeptides for use in tumor therapy, for example, in vaccines.

However, if arguendo, the PTO were considered to have met its burden of proof, Applicants respectfully point to rebuttal evidence in the Specification at page 75, line 14 to page 76, line 21, which refers to the experiments of Uemura et al. as examples of the use of MN-specific anti-idiotype antibodies as anti-tumor vaccines as envisioned in Zavada et al.'s '676 patent at column 25, lines 1-3. The Specification states at page 75, liens 14-19: "MN-specific anti-idiotypic antibodies have therapeutic utility as a vaccine for neoplastic disease associated with abnormal MN expression. . . . Those therapeutic utilities are demonstrated by research done with the MN-specific G250 MAb, and anti-idiotype antibodies thereto (Ab2) . . . as demonstrated by the studies described below."

The Uemura et al. studies therapeutic described in the Specification at page 75, line 20 to page 76, line 21 are incorporated as evidence of the therapeutic utility of MN-specific anti-idiotype antibodies. Applicants respectfully submit that the incorporated examples and remarks in the Specification at page 75, line 11 to page 76, line 21 provide evidence of the in vivo therapeutic utility of anti-idiotypic antibodies specific to MN-specific antibodies. That evidence alone is sufficient to rebut any argument that one of skill in the art would doubt the enablement of the MN-specific anti-idiotype therapy of the claimed invention.

II. Pioneering Invention Entitled to Broad Claims.

In addition to the above arguments, Applicants respectfully submit that the pioneering nature of the instant invention entitles the Applicants to broad claim coverage. Applicants respectfully point out that they were the first people to discover the MN gene, MN protein, MN-specific antibodies and by right and inherently MN-specific anti-idiotype antibodies, and the oncogenic nature of MN. Therefore, the Applicants are pioneers concerning MN as well as MN's diagnostic, prognostic and

therapeutic uses. As the Court of Customs and Patent Appeals (CCPA) stated in In re Hogan and Banks, 194 USPQ 527 at 537 (CCPA 1977):

> As pioneers . . . they . . . deserve broad claims to the broad concept. What were once referred to as 'basic inventions' have led to 'basic patents,' which amounted to real incentives, not only to invention and its disclosure, but to its prompt, early disclosure.

If only claims to anti-idiotypic antibodies to antibodies that specifically bind to the specific amino acid sequence deduced from the specific cDNA sequence that was isolated by the Applicants were issued, anyone could avoid infringement of such a claim by modifying SEQ ID NO: 1 slightly by techniques known in the art to code for MN proteins and MN polypeptides substantially similar to SEQ ID NO: 2 and fragments thereof, or by substituting equivalent codons in SEQ ID NO: 1, such that the substituted version would express the same MN protein or MN polypeptide, or by both modifying the sequence slightly and substituting equivalent codons.

An unduly narrow claim limited to SEQ ID NO: 2 would require that Applicants essentially dedicate their invention to the public, since ones of skill in the art could easily avoid infringement of the claim. If a narrow claim to MN-specific anti-idiotype antibodies, limited to anti-idiotype antibodies binding the idiotopes of antibodies, which bind to epitopes of MN antigen deduced from a particular isolated sequence, is all the discoverers of a putative oncogene and oncoprotein, and its utilities can obtain, then the opportunity for obtaining a basic patent upon early disclosure of pioneer inventions would be abolished. Consequently, the purposes underlying the patent laws to promote early disclosure of pioneer inventions and progress in science would be undermined.

Applicants by being the first to isolate the MN gene and protein and related materials have provided valuable research tools to the medical research community that add greatly to the understanding of tumorigenicity and the neoplastic process. The U.S. Constitution recites that patents are granted "to promote the progress of science and the useful arts by securing for limited times to . . . inventors the exclusive right to their respective . . . discoveries." Applicants respectfully submit that

the goal of the Constitution quoted above would not be served by limiting Applicants to the precise amino acid sequence deduced from the cDNA sequence isolated by them.

The Examiner is respectfully referred to In re Goffe, 191 USPQ 429, 431 (CCPA 1976), wherein the CCPA criticized the U. S. Patent and Trademark Office for attempting to limit the appellant to specific claims, lest a competitor seeking to avoid infringement could achieve this goal readily by merely following the disclosure in the patent when it issues. The CCPA further stated:

> [T]o provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found will work . . . would not serve the constitutional purpose of promoting progress in the useful arts.

[Emphasis added.]

III. Claims of Reasonable Scope Commensurate with Enablement.

Applicants respectfully conclude that the claims have been amended to point out with particularity and clarity the subject matter regarded by the Applicants as their invention, and provide a reasonable scope, that is, closely related to SEQ ID NOS: 1 and 2. The independent claims -- Claims 22, 30 and 42 -- all refer to MN proteins and polypeptides which are defined in the Specification, as set forth in detail above, as being substantially homologous to the MN protein represented by SEQ ID NO: 2, having similar epitopes, and being translated from nucleotide sequences that have an 80-90% homology to SEQ ID NO: 1, that is, hybridize to the complement of SEQ ID NO: 1 under stringent hybridization conditions.

Applicants respectfully conclude that the instant application reasonably conveys to ones of skill in the art that the Applicants at the time of filing the application had possession of the claimed invention, and that the instant application meets the written description and enablements requirement of 35 USC 112, first paragraph. Applicants respectfully request that the Examiner reconsider and withdraw this rejection in view of the above amendment and remarks.

35 U.S.C. Section 112, First Paragraph Rejection of Claims 23 and 31 (Section 11 of Office Action)

Claims 23 and 31 stand rejected under 35 U.S.C. Section 112, first paragraph, because

> the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.
>
> . . . Therefore, a suitable deposit for patent purposes is suggested.

[Office Action, Section 11, page 10.] Applicants respectfully respond that the hybridomas VU-M75 and MN 12.2.2 were deposited at the American Type Culture Collection (ATCC) under ATCC Nos. HB 11128 and HB 11647, respectively, under provisions that satisfy the requirements of 37 CFR 1.801-1.809.

Applicants respectfully point out that the instant application states at page 116, line 31 to page 117, line 14, that the deposits of the VU-M75 and MN 12.2.2 hybridomas were

> made under the provisions of the Budapest Treaty on the International Recognition of Deposited Microorganisms for the Purposes of Patent Procedure and Regulations thereunder (Budapest Treaty). . . . The hybridomas . . . will be made available by the ATCC under the terms of the Budapest Treaty, and subject to an agreement between the Applicants and the ATCC which assures unrestricted availability of the deposited hybridomas . . . to the public upon the granting of patent from the instant application.

[Emphasis added.]

The specification at page 117, lines 11-12 indicates that the VU-M75 hybridoma was deposited at the ATCC on Sept. 17, 1992 under ATCC # HB 11128, and that the MN 12.2.2 hybridoma was deposited at the ATCC under ATCC # HB 11647 on June 9, 1994. The deposit of the VU-M75 hybridoma at the ATCC was made before the filing of the earliest U.S. priority application for the instantly claimed invention, that is,

before Oct. 21, 1992 [the filing date of U.S. Serial No. 07/964,589, now U.S. Patent No. 5,387,676 (issued Feb. 7, 1995); "the '676 patent"].

The completed name and address of the American Type Culture Collection (ATCC) can be found at page 116, lines 31-33 of the instant specification. Enclosed as Appendix B are copies of the ATCC Deposit Receipts which indicate that the hybridomas VU-M75 and MN 12.2.2, which produce monoclonal antibodies M75 and MN12, respectively, were deposited under the terms of the Budapest Treaty on September 17, 1992 and June 9, 1994, respectively. The Manual of Patent Examining Procedure (MPEP) states at the end of Section 2410.01 under the heading "Conditions of Deposit," that "the mere indication that a deposit has been made under conditions prescribed by the Budapest Treaty would satisfy all conditions of these regulations except the requirement that all restrictions on access be removed on grant of the patent. Ex parte Hildebrand, 15 USPQ2d 1662 (Bd Pat. App. & Int. 1990)." As the last sentence of the above-quoted paragraph of the instant application indicates, the Applicants stated that their agreement with the ATCC "assures unrestricted availability of the deposited hybridomas . . . to the public upon the granting of patent from the instant application."

However, to provide further assurance that all the requirements concerning the hybridoma deposit are met, the undersigned Attorney for the Applicants states:

> By signing below the Attorney for the Applicants certifies that:
>
> > (a) during the pendency of this application, access to the deposits of the hybridomas VU-M75 and MN 12.2.2, deposited at the American Type Culture Collection (ATCC) at 10810 University Blvd., Manassas, Virginia 20110-2209 (USA) under the ATCC designations HB 11128 and HB 11647, will be afforded to the Commissioner upon request;
> >
> > (b) all restrictions imposed by the depositor on the availability to the public of the hybridomas VU-M75 and MN 12.2.2 will be irrevocably removed in accordance with 37 CFR 1.808 upon the granting of a patent from the instant application;

> (c) the deposits of the hybridomas VU-M75 and MN 12.2.2 will be maintained in the ATCC for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited hybridomas, whichever is longest; and
>
> (d) the deposits of the hybridomas VU-M75 and MN 12.2.2 will be replaced if they should become nonviable or non-replicable. . . .

The first time that the hybridoma MN 12.2.2 was disclosed in the string of priority applications claimed for the instant invention was in U.S. Serial No. 08/260,190 filed June 15, 1994 (now allowed, issue fee paid). The MN 12.2.2 hybridoma was deposited at the ATCC before the filing of U.S. Serial No. 08/260,190, and was in the Applicants' possession before that filing. By signing below, the Attorney for the Applicants declares that the MN12.2.2 hybridoma described in U.S. Serial No. 08/260,190, in the instant specification and in all the intervening priority applications is identical to the MN 12.2.2 hybridoma deposited at the ATCC under ATCC # HB 11647 on June 9, 1994.

Applicants respectfully conclude that the deposits of hybridomas VU-M75 and MN 12.2.2 at the ATCC under the terms of the Budapest Treaty in view of the above-quoted statements made by the undersigned Attorney for the Applicants are sufficient to meet all the requirements for deposits imposed by 37 CFR 1.801-1.809. Applicants respectfully request that the Examiner reconsider and withdraw the instant 35 U.S.C. § 112, first paragraph rejections of Claims 23 and 31.

Claim to Priority (Section 12 of Office Action)

> The Office Action states at pages 14 to 15 under Section 12 that
>
> The filing date of the instant claims is deemed to be the filing date of parent application USSN 08/177,093, i.e., 12/30/1993 (now U.S. Patent 6,051,226). It is noted that priority application Czechoslovakian patent Application PV-709-92; filed 3/11/1992 is not available to the examiner at

> this time. Priority application USSN 07/964,589 (now U.S. Patent 5,387,676) does not apparently support the claims of the instant application. The MN sequence (cDNA and amino acid sequence) disclosed in U.S. Patent 5,387,676 . . . diverges from the instantly claimed MN sequence (cDNA and amino acid sequence) beginning at amino acid residue 411. . . .

[Emphasis added.]

Zavada et al. '676 Patent

Applicants respectfully but most forcefully traverse those statements, first pointing out that the earliest U.S. priority application, that is, the great, great, great, great grandparent of the instant application filed on October 21, 1992, now U.S. Patent No. 5,387,676 ("the '676 patent") enables the claimed invention. As indicated above in detail in the REMARKS section under the Amendments to the Claims subsection, in the response to the 35 U.S.C. Section 112, First Paragraph Rejection (Sections 8-9 of the Office Action), support for the claimed invention can be found in the '676 patent in view of what was conventionally known in the art at the time of filing the '676 patent, that is, on Oct. 21, 1992, wherein that conventional art is represented by by the cited Raychaudhuri et al., reference as pointed out by the Examiner. Applicants rely on the above discussion of the '676 patent to show support therein in view of what is conventional in the art, but highlight below a few significant points from the above-detailed comments concerning the '676 patent.

The Zavada et al. '676 patent states at least at column 25, lines 1-3: "It will further be appreciated that anti-idiotype antibodies to antibodies to MN proteins/polypeptides are also useful as vaccines and can be similarly formulated." Applicants respectfully point out that in view of the disclosure of the '676 patent [which provides the MN cDNA sequence and deduced amino acid sequence, which were corrected by Declarations of the inventors (Zavada et al.) in view of the ATCC deposit of the VU-M75 hybridoma; please see Appendix E for the corrected amino acid and cDNA sequences], and in view of what was conventionally known in the art at the priority date of the patent, one of skill in the art would know how to make and use the instantly claimed MN-specific anti-idiotype antibodies.

One of skill in the art would see that inherent in the statement at column 25, lines 1-3 of the Zavada et al. '676 patent is the necessity that the anti-idiotype antibodies to antibodies to MN proteins/polypeptides must mimic MN proteins/polypeptides to be useful, as MN protein/polypeptides would be, when formulated in a vaccine. Applicants respectfully point out that a "specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

The Office Action itself points out that it was well known in the art at the time of the earliest priority date for the subject invention how to make and use anti-idiotype antibodies once an immunogenic protein/polypeptide has been identified. The Office Action states at page 8:

> The art teaches that the process of generating internal image anti-idiotype antibodies are well known to those of skill in the art and can result in the production of internal image antibodies that mimic the immunological properties of the initial antigen (i.e., tumor antigen or infectious agent). For support, See Raychaudhuri S., U.S. Patent 5,270,202, bridging paragraph of columns 2-3).

The cited Raychaudhuri, S. '202 patent was filed on March 12, 1991, and a number of references cited in the '202 patent (particularly in the paragraph bridging columns 2-3) provide evidence of the conventionality in the art of making and using anti-idiotype antibodies well before the earliest priority date for the instantly claimed MN-specific anti-idiotype antibodies.

The Office Action contends that the MN cDNA and amino acid sequence of the '676 patent are not the same as those of the instant application. Applicants respectfully direct the Examiner's attention to Appendix E which comprises the Certificate of Corrections for the '676 patent, showing that the cDNA and amino acid sequences of the '676 patent were corrected [by Declarations from the inventors (Zavada et al.) correcting errors in the original cDNA sequencing (primarily common GC

compressions) in view of the deposit at the ATCC of the VU-M75 hybridoma that secretes the M75 mab].

Applicants respectfully conclude that the Zavada et al. '676 patent, the earliest U.S. priority application claimed by the instant application, has been shown to support the claimed invention in view of what was conventionally known in the art as of its filing date. Applicants respectfully request that the Examiner reconsider the priority accorded the claimed invention in view of the above remarks and Appendix E and accord the subject invention at least its rightful priority of Oct. 21, 1992 (filing date of the '676 patent).

Czechoslovakian Patent Application PV-709-92 (filed March 11, 1992) Antedates Pastorekova et al., **Virology**, 187(2): 620-626 (April 1992)

A certified translation of the Czechoslovakian patent application (filed March 11, 1992) is enclosed as Appendix C.

Also enclosed as Appendix D is the cover page of the issue of Virology that contains Pastorkova et al., Virology 187(2): 620-626 (April 1992) that was received, as indicated by the date stamp, by the Biosciences Library of the University of California at Berkeley on April 2, 1992. Applicants respectfully question why that April 1992 issue of Virology would lead the Examiner to cite to the Pastorekova et al. article at the top of page 16 of the Office Action with the date "3/9/1992"?

Applicants respectfully submit that the Czechoslovakian priority application is sufficient to antedate any information concerning the MN gene and protein that is found in the Pastorekova et al. April 1992 article, and is more enabling than that 1992 article. The Czechoslovakian priority application indicates in its third paragraph that the VU-M75 hybridoma that secretes the M75 monoclonal antibody ("M75 mab") was deposited in the Collection of hybridomas of the Institute of Virology, Slovak Academy of Sciences, Dubravska cesta 9, 842 46 Bratislava and that the M75 mab has an IgG2B isotype. Applicants respectfully conclude that the information in the cited Pastorekova et al. April 1992 article concerning the MN gene and protein, and M75 monoclonal antibody is covered in the Czechoslovakian priority application, and that Pastorekova et al. is therefore not applicable to the subject claims.

Applicants respectfully further conclude that the instant application rightfully claims priority from the Czechoslovakian patent application for all that it discloses in support of the instantly claimed invention.

35 U.S.C. Section 103 Rejections (Sections 13-17 of Office Action)

Common Ownership (Section 14 of the Office Action)

The Office Action states at page 15 that "Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a)." [Office Action, Section 14.]

Applicants are respectfully aware of their duty under 37 CFR 1.56 concerning reporting lack of common ownership of any claimed aspects of the invention at the time it was made. Applicants respectfully declare that the invention as claimed was commonly owned at the time all claimed aspects were made.

References Cited in 103 Rejection in Sections 15-17 of the Office Action

The Office Action cites the following references in the 103 rejections of Sections 15-17:

Pastorekova et al., Virology, 187(2): 620-626 (April 1992);

Pastorek et al., Oncogene, 9: 2877-2888 (1994);

Raychaudhuri et al., J. Immunol., 13 (5): 1743-1749 (1986);

Oosterwijk et al., WO 88/08854 (Nov. 17, 1988);

Uemura et al., Brit. J. Cancer, 81(4): 741-746 (1999);

Raychaudhuri et al., J. Immunol., 139(1): 271-278 (1987); and

Oosterwijk et al., Int. J. Cancer, 38: 489-494 (1986).

To avoid repetition in the context of each of the 103 rejections of Sections 15-17 of the Office Action, each of the references will be discussed individually to show that each of the references is either simply not prior art to the claimed invention, or is not enabling prior art. Thus, Applicants respectfully submit that the references either

individually or in any combination cannot render the instantly claimed invention either anticipated or obvious.

Pastorekova et al. April 1992

As discussed above in the Priority section of this response, Pastorekova et al. April 1992 is antedated by the Czechoslovakian priority application filed on March 11, 1992 by the Applicants. Not only is Pastorekova et al. not prior art to the claimed invention, but even if it were hypothetically considered to be prior art in any aspect, it is not enabling prior art.

The '676 patent not only contains all the relevant disclosure of Pastorekova et al. but also discloses a 1397 base pair MN cDNA sequence as well as nucleotide sequences that hybridize to it under stringent hybridization conditions. Further, that earliest U.S. priority application (now the '676 patent) was accompanied by the deposit at the ATCC of the VU-M75 hybridoma that secretes the M75 monoclonal antibody that specifically binds to MN protein.

If Pastorekova et al. should not be considered to enable the claimed invention, Applicants respectfully point out that it can not be applied effectively against the instant claims. As stated in Ciba-Geigy Corp. v. Alza Corp., 33 USPQ2d 1018 (D.N.J. 1994), aff'd in part, vacated in part, 68 F.3d 487 (Fed. Cir. 1994) (unpublished): "[A]nticipation and obviousness require that the prior art teach an operative apparatus". [See also Beckman Instruments, Inc. v. LKB Produkter AB, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989), aff'd, 930 F.2d 37 (Fed. Cir. 1991) (unpublished): "In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."]

Whereas the '676 patent enables the claimed invention, Pastorekova et al. does not. There is no MN amino acid or nucleotide sequence data in Pastorekova et al. There is insufficient description in Pastorekova et al. to prepare the M75 mab. The material in Pastorekova et al. is incorporated in the '676 patent. If Applicants could have described how to make the M75 mab, Applicants would not have deposited the VU-M75 hybridoma that secetes the M75 mab at the ATCC. No one of skill in the art could identify the MN gene and protein without an MN-specific antibody.

As indicated below, the Oosterwijk et al. group which had the G250 monoclonal antibody took years to isolate and sequence the G250 antigen which they finally found to be identical to the MN antigen, and they had a monoclonal antibody to the antigen they were seeking to isolate and sequence. It would be very implausible that one of skill in the art could isolate the MN gene and protein without a MN-specific monoclonal antibody.

Applicants respectfully conclude that Pastorekova et al. is not prior art to the claimed invention in view of the antedating Czechoslovakian priority application (Appendix C) which is more enabling than is Pastorekova et al., and that even if Pastorekova et al. were in some aspect hypothetically considered to be prior art, that it is nonenabling prior art.

Pastorek et al. 1994

Applicants also respectfully submit that Pastorek et al. (1994), published after the priority data of the instant application, cannot overcome the lack of enablement of Pastorekova et al. (1992) for the instant claims. As presented above by the Applicants in response to Section 12 of the Office Action ("Priority"), the instant claims are entitled to a priority date of at least Oct. 21, 1992. Therefore, Pastorek et al., with a 1994 publication date, cannot be considered prior art against the instant claims.

Uemura et al. 1999

For the reasons cited above for Pastorek et al. 1994, since the claimed invention has a priority date of at least to Oct. 21, 1992 (filing date of the '676 patent), the Uemura et al.1999 reference is not prior art. Applicants respectfully conclude then that Uemura et al. 1999 cannot be applied in an obviousness rejection.

Oosterwijk et al 1986 and 1988

Oosterwijk et al. 1986 and 1988 (WO 88/08854) discuss the following biological materials:

- 5 monoclonal antibodies ("mabs") to renal cell carcinomas ("RCCs"), one of which is a monoclonal antivody ("Mab") termed "G250"

- 5 antigens associated with RCC, one of which is an antigen termed "G250"
- hybridomas secreting the above 5 monoclonal antibodies.

However, the Oosterwijk references do not describe how to reproducibly obtain the G250 Mab, as they insufficiently disclose the antigen to which the G250 Mab binds. The Oosterwijk references provide no biochemical characteristics about the G250 antigen. Oosterwijk et al. 1988 at page 18, lines 15-16 "suggests that G250 recognizes a protein." [Emphasis added.] A document can only be considered as relevant state of the art if it describes a technical teaching that can be reproduced properly by one of skill in the art. Such a technical teaching on how to reproducibly obtain the G250 Mab is not so disclosed in the Oosterwijk references, and with respect to that issue, the Oosterwijk references are not enabling prior art that can be used under 35 USC 103.

The only characterization of the G250 antigen that is supplied in the Oosterwijk references is what could have been deduced from the immunoreactivity of the G250 Mab. However, the immunoreactivity of the G250 Mab as reported by the Oosterwijk references is distinctly different from the immunoreactivity of the MN-specific antibodies of the present invention.

Whereas the Oosterwijk references describe the G250 Mab as basically being specific to kidney carcinoma [i.e., renal cell carcinoma (RCC)], and having low or no reactivity with cancers of most other organs, the MN-specific antibodies of the present application are strongly associated with cancers of many different organs. [Compare, for example, Oosterwijk et al. 1988 at page 7, lines 7-10 with the present application at page 2, line 29 to page 3, line 21 (cervical and colorectal lesions)]. Further, Oosterwijk et al. 1988 indicates that if the G250 Mab stained non-RCC tumor cells, the staining was cytoplasmic [page 18, lines 27-29], but the staining of RCC tumor cells was membranous [page 19, lines 22-27]. In contrast, the present application at page 19, lines 1-2 discloses that the MN protein is "located at the cell surface, although in some cases it has been detected in the nucleus."

Only in 1997, years after the priority date of the present application, and further years after the M75 Mab of claim 23 of the present application became publicly available from an international depository, did the inventors/authors of the Oosterijk et al. references and Uemura et al. report that the G250 antigen "is identical to MN, a

tumor-associated antigen identified in cervical carcinoma (Pastorek et al. 1994). This antigen (G250, MN) is a transmembrane glycoprotein of 54/58 kDA and detectable in several types of malignancies. . . ." [Uemura, J. Urology 157: 377 (1997); emphasis added.]

Whatever characterization of the G250 antigen, that could have been deduced from the immunoreactivity of the G250 mab reported in the Oosterwijk references is very different from the characterization of the MN protein disclosed in the '676 priority patent and in the instant application. Oosterwijk et al. admit in 1997 in the above quote that the G250 antigen is a "tumor-associated antigen identified in cervical cancer [by Zavada et al.]" and is a "transmembrane glycoprotein . . . detectable in several types of malignancies." However, Oosterwijk et al. describe the immunoreactivity of the G250 mab as predominantly RCC-specific, having low or no reactivity with most other malignancies, and staining the membranes of only RCC tumor cells, and if staining at all non-RCC tumor cells, staining the cytoplasm of such non-RCC tumor cells.

The Oosterwijk references cannot anticipate or render obvious the claims of the present application since the G250 antigen is, not only, not identified therein by any biochemical characteristics, but also whatever characterization that could be deduced about the G250 antigen from the G250 mab's immunoreactivity reported in the Oosterwijk reference is very different from the actual characterization of the MN protein disclosed in the '676 patent and in the instant application.

In the following, Applicants will first of all point out that the subject-matter described in the Oosterwijk references do not contain an enabling disclosure for either the G250 antigen or the G250 mab. Applicants respectfully conclude that as the Oosterwijk references are not enabling, they are not enabling prior art and cannot then be applied against the present application either for novelty or for obviousness.

Not only do the Oosterwijk references not provide an enabling disclosure of the G250 antigen, but they also provide substantially incorrect indications concerning the potential identity of the G250 antigen. One of skill in the art relying upon the Oosterwijk references would not associate the G250 antigen with the MN protein, the

Oosterwijk references then cannot anticipate nor can they render obvious the claims of the present application, alone or in any combination with other prior art reference.

In Oosterwijk 1988, an antigen named G250 is described as "present on RCC . . . and absent from . . . most malignancies." [Page 2, lines 12-16.] Oosterwijk 1988 states that "[t]he sensitivity to proteinase K suggests that G250 recognizes a protein." [Page 28, lines 15-16; emphasis added.] As indicated above, the Oosterwijk references do not even clearly identify the G250 antigen as a protein, and certainly does not provide any inkling of what the amino acid sequence of that protein would be, if it were a protein. Further, the Oosterwijk references provide no biochemical characterization of the G250 antigen whatsoever – no isoelectric point, no molecular weight, no indication of whether the antigen is glycosylated or not – no biochemical characteristics at all.

The inventors of Oosterwijk et al. were not able to identify the G250 antigen until long after the publications of Zavada et al. made information regarding the MN protein and MN-specific antibodies publicly available. To summarize, the antigen G250 is not reproducibly described by the Oosterwijk references for one skilled in the art and therefore not sufficiently disclosed.

Disclosure of the monoclonal antibody G250

The Office Action takes the position that the G250 Mab specifically binding to the G250 antigen, renders obvious the subject claims anti-idiotype antibodies to MN-specific antibodies (i.e., claims 22, 30, 36-38, 42-43, 46-48 and 52).

Conventional methods were used to produce the G250 hybridoma, that secretes the G250 mabs as described in Example 1 of Oosterwijk et al. 1988 as well as in Oosterwijk et al. 1980: a mouse was immunized with cell homogenates from primary RCC lesions. The spleen cells were isolated and fused with Sp2/0 myeloma cells. Hybridomas were selected by picking up spots on a RCC coated filter and were grown in suspension. "Tissue culture medium from these clones was tested on cryostat sections of RCC lesions and normal kidney. Clones reacting with RCC and not with normal kidney tissue were subcloned and tested on other normal tissues." [Oosterwijk et al. 1988, p. 16, lines 7-11.]

At any one time, perhaps about 100,000 proteins are being expressed in a cell, and thousands of proteins are being expressed on the surface of a cell. There were then sure to be a great number of antigens in the cell homogenate used for immunization in the above process. Further, the G250 antigen would be expected to have several different epitopes. It is obvious that the above method of producing hybridomas and screening antibodies would produce a very large spectrum of different antibody secreting hybridomas.

Oosterwijk et al. 1986 also state on page 493 (col. 2) that "endogenous or exogenous retrovirus expression in RCC . . . may explain the relatively large number of new antigens in RCC." [Emphasis added.] The described process for the production of a G250 hybridoma does not enable the skilled artisan to determine, to which of the huge number of antigens in RCC cell homogenates the secreted G250 mabs are specific.

Further, Oosterwijk et al. 1986 supports that there are a wide variety of mabs that stain RCC but do not stain normal kidney tissue. In Oosterwijk et al. 1986, it is stated that the G250 mab recognizes an antigen preferentially expressed on cell membranes of RCC and not expressed in normal proximal tubular epithelium. In the discussion [see page 493], Oosterwijk et al. 1986 cite to several other references. All of those references deal with mabs developed against RCC. Oosterwijk et al. 1986 noted that "it is seen that only antibodies S22 . . . [Ueda et al., PNAS (USA), 78(8): 5122-5126 (Aug.1981)], D5D . . . [Vesella et al., Cancer Res., 45: 6131-6193 (Dec. 1985)], and B7, C8, D8 and E6 . . . [Schärfe et al., Eur. Urol., 11: 117-120 (1985)] stain RCC, while they do not stain normal proximal epithelium."

In their 1986 article, Oosterwijk et al. distinguish the G250 mab from the other RCC-specific mabs that do not react with normal renal tissue only by the staining patterns of the various mabs. For example, Vesella et al.'s D5D mab stained 14 of 19 RCC (74%) in contrast to the G250 mab which stained 53 of 55 RCC (98%), and Schärfe's mabs, although staining as high a percentage of RCC as the G250 mab, do not stain sarcomatous RCC in contrast to the G250 mab [see page 493, top of column 2.]

From the foregoing, it is clear that Oosterwijk et al. do not reproducibly disclose the true nature of what they call the "G 250 mab". The authors were unable to draw a clear dividing line between the above-mentioned mabs and the G250 mab.

Oosterwijk et al. in "Immunohistochemical Analysis of Monoclonal Antibodies to Renal Antigens: Application in the Diagnosis of Renal Cell Carcinoma," Am. J. Pathol., 123(2): 301-309 (May 1986) (IDS submitted on 10/17/01) at page 307 (column 2) discuss mabs to RCC -- RC3, RC 38, RC 69 and RC 154 -- which mabs are claimed in the Oosterwijk et al. application (WO 88/08854). That article refers to "[o]ther investigators [who] have also described Mabs with a high specificity for RCC. . . . [citations admitted]," and admit that "[a] comparison between the Mabs described in this study with Mab's against renal antigens described by others is difficult, partly because of different assay methods." [Emphasis added.] If it is difficult to distinguish RCC-specific mabs from one another by their staining patterns, what would the staining pattern of a RCC-specific mab suggest about another mab that was known not to be RCC-specific and to have otherwise very different immunoreactivity than that reported for the RCC-specific mab?

From the foregoing, it is clear that the Oosterwijk references do not reproducibly disclose the true nature of what they call the "G 250 mab". All the claims of Oosterwijk et al. 1988 are directed to RCC; cancer of no other organ is mentioned in the claims. The title of Oosterwijk et al. 1988, "Monoclonal Antibodies to Renal Cell Carcinoma" highlights the RCC-specificity of the G250 mab.

A deposit of the hybridoma that secretes the G250 mab with a recognized depositary institution might have provided enabling disclosure of its nature. No such deposit occurred in conjunction with the Oosterwijk et al. 1988 application. The Examiner of the Oosterwijk et al. 1988 application indicated on page 3 of the first Communication that " . . . the monoclonal antibody producing hybridomas of the application are not deposited and thereby not reproducible. . . . In this respect, the application does not fulfill the requirement of Article 83 regarding the disclosure of microorganisms as set out in Rule 28 EPC."

From the foregoing, it is clear that the subject matter of the Oosterwijk references are not sufficiently disclosed, enabling the skilled artisan to carry out their

teaching. Not only do the Oosterwijk references not anticipate or render obvious the claimed invention, alone or in conjunction with any other prior art reference, those references teach away from the identity of the G250 antigen with the MN antigen as shown above.

The Office Action at page 21 states that "[t]he G 250 antigen is also expressed in several other tumor types" (i.e., other than RCC). Figure 3 of Oosterwijk et al. 1986 does show that the G 250 MAb stained some tumor types other than RCC. However, in non-RCC tumors "the fraction of tumors stained, the percentages of G 250-positive tumor cells and the intensity of staining were generally much lower." [Oosterwijk et al. 1986, page 492, column 1, first full paragraph.] Also, as in the Oosterwijk et al. application WO 88/08854, Oosterwijk 1986 indicates that if the G250 Mab stained non-RCC tumor cells, the staining was always cytoplasmic [page 492, column 1, first full paragraph], but the staining of RCC tumor cells was membranous [page 490, column 2, last full paragraph]. The present application, however, discloses that the MN protein is "located at the cell surface, although in some cases it has been detected in the nucleus." [Instant application, page 19, lines 1-2.]

Although Oosterwijk et al. 1988 does note at page 6, lines 17-26 that "the G250 determinant was also found in nonRCC tumors" and that G250 stains a variety of other tumors, although at low incidence. . . ." [emphasis added.], it reports at page 18, lines 24-27, that the fraction of non-RCC "tumors stained, the percentage of G250 positive tumor cells and the intensity of staining were generallly [*sic*] much lower [than in RCC]." Oosterwijk et al. 1988 then lists at page 19, lines 1-9 the following non-RCC tumors that had no reactivity with the G250 mab – two Wilm's tumors, one prostatic carcinoma, five gastric carcinomas, and two liver cell carcinomas.

The paragraph bridging pages 4-5 of Oosterwijk et al. 1988 describes the bar histogram of Figure 4 showing the results of staining a number of malignant tumors with the G250 mab. Whereas Figure 4 shows 90% and 63% of the RCC, primary and metastic tumor cells, respectively, to have 50% or more of the tumor cells stained, only 8% of colonic cancers, 5% of sarcomas, 5% of ovarian cancers and no mammary, pulmonary, testicular or melanoma cancers showed such staining.

The results of staining the metastases of non-RCC tumors are not shown in Figure 4, but are described in Oosterwijk et al. 1988 at page 5, lines 6-12: "The metastases were: nine mammary tumors (one with less than 1% tumor cells positive, eight negative), four pulmonary tymors (all negative) and four colonic tumors (one with more than 50% positive tumor cells, onw [*sic*] with less than 1% tumor cells positive, two negative)."

Oosterwijk et al. at page 18, lines 27-28 state: "The staining of positive non RCC tumor cells always appear to be cytoplasmatic." [Emphasis added.] Then, at page 19, lines 11-13 reports: "In two renal adenomas . . . all cell membranes were stained."

Those quotes from Oosterwijk et al. 1988 indicate that if stained with the G250 mab, the staining of non-RCC tumor cells was cytoplasmic, whereas the staining of renal cancer cells was membranous. In contrast, the present application as indicated above states that the MN protein is located on the cell surface and sometimes in the nucleus.

The Oosterwijk references cannot anticipate or render obvious the claims of the present application since the G250 antigen is, not only not identified by any biochemical characteristics, but also whatever characterization that could be deduced about the G250 antigen from the G250 Mab's immunoreactivity reported in the Oosterwijk references are very different from the actual characterization of the MN protein disclosed and claimed in the present application. One of skill in the art relying upon Oosterwijk would not associate the G250 antigen with the MN protein disclosed and claimed in the present application. Further, the Oosterwijk et al. references are evidence of the nonobviousness of the instant invention.

Raychaudhuri et al. 1986 and 1987

None of the cited Raychaudhuri et al. references contain any disclosure concerning the MN protein, and certainly contain no disclosure concerning an anti-idiotype antibody to an antibody that specifically binds to MN proteins/polypeptides. As explained above, the other references cited in the 103 rejection are either not prior art or are not enabling prior art. Applicants respectfully conclude that the Raychaudhuri et al.

references alone, without a reference disclosing the MN amino acid or cDNA sequence, cannot render the instantly claimed invention obvious.

Cited References Cannot be Combined to Anticipate or Render Obvious the Instantly Claimed Invention

For the reasons detailed above for each of the references cited in the Office Action for the 103 rejections in Sections 15-17, none of the references alone or in combination with any other can render the instantly claimed invention obvious. The references are either simply not prior art, as Pastorekova et al. April 1992, Pastorek et al. 1994 and Uemura et al. 1999, or are not enabling, as Pastorekova et al. April 1992 and the Oosterwijk et al. 1986 and 1988 references. Not only are the Oosterwijk et al. references not enabling, but they also provide evidence of the nonobviousness of the instant invention by the difficulty and years they took to isolate the G250 antigen and identify it with the MN protein. Further, the Oosterwijk et al. references teach away from identifying the MN protein with the G250 antigen.

The Raychaudhuri et al. references disclose nothing about the MN protein, which had not yet been discovered by Zavada et al. The Raychaudhuri et al. references provide instead evidence of what was conventionally known in the art about making and using anti-idiotype antibodies, well before the instant application's earliest U.S. priority date – Oct. 21, 1992.

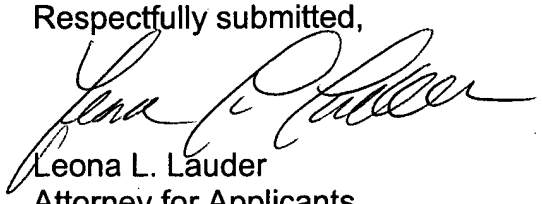
Applicants respectfully conclude that none of the references alone or in any combination render the instantly claimed invention obvious.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claim amendment be entered, and that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the

Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



Leona L. Lauder
Attorney for Applicants
Registration No. 30,863

Dated: July 22, 2004

27, drawn to a MN-specific antibody, classified in class 530, subclass 387.1."]

Appendix 1 shows the amendments made to Claims 22-27 of the parent application. Applicants respectfully submit that those amendments and the addition of new Claims 30-52 are made to point out with more particularity and clarity the subject matter regarded by the Applicants as their invention, and that no new subject matter has been added by those amendments and new claims.

Support in the Specification concerning anti-idiotype antibodies to MN-specific antibodies and anti-anti-idiotype antibodies to such anti-idiotype antibodies can be found at least at page 12, line 29 to page 13, line 31; at page 15, lines 24-33; at page 75, line 11 to page 76, line 21; at page 81, lines 27-32; and at page 122, lines 9-12.

The amendment to Claim 22 specifies with particularity and clarity the term "MN-specific antibody," and that terminology reflected in new Claims 30-52 is supported throughout the Specification, e.g., at least at page 7, line 12 to page 15, line 14; more specifically, e.g., at least at page 7, lines 12-20, at page 9, lines 18-24, at page 10, lines 15-24, at page 12, lines 29-31, at page 13, lines 12-18, at page 13, lines 27-31 and at page 14, lines 4-5.

American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: (301)231-5520 Telex: 898-055 ATCCNORTH • FAX: 301-770-2587

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Triton Diagnostics, Inc.
Attention: George B. LaMotte, III, Ph.D.
1401 Harbor Bay Parkway
Alameda, CA 94501

Deposited on Behalf of: Triton Diagnostics, Inc.

Identification Reference by Depositor: ATCC Designation

Hybridoma, VU-M75 HB 11128

The deposit was accompanied by: ___ a scientific description ___ a proposed taxonomic description indicated above.

The deposit was received September 17, 1992 by this International Depository Authority and has been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested September 22, 1992. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. MacLaren

Bobbie A. Brandon, Head, ATCC Patent Depository Date: September 23, 1992

cc: Leona L. Lauder

Form BP4/9

American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: (301)231-5520 Telex: 898-055 ATCCNORTH • FAX: 301-770-2587

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Ciba Corning Diagnostics Corporation
Attention: Marian Sacco
1401 Harbor Bay Parkway
Alameda, CA 94502

Deposited on Behalf of: Ciba Corning Diagnostics Corporation

Identification Reference by Depositor:	**ATCC Designation**
Hybridoma, MN 12.2.2	HB 11647

The deposit was accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposit was received June 9, 1994 by this International Depository Authority and has been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 10, 1994. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. Brandon **Date:** June 14, 1994

Bobbie A. Brandon, Head, ATCC Patent Depository

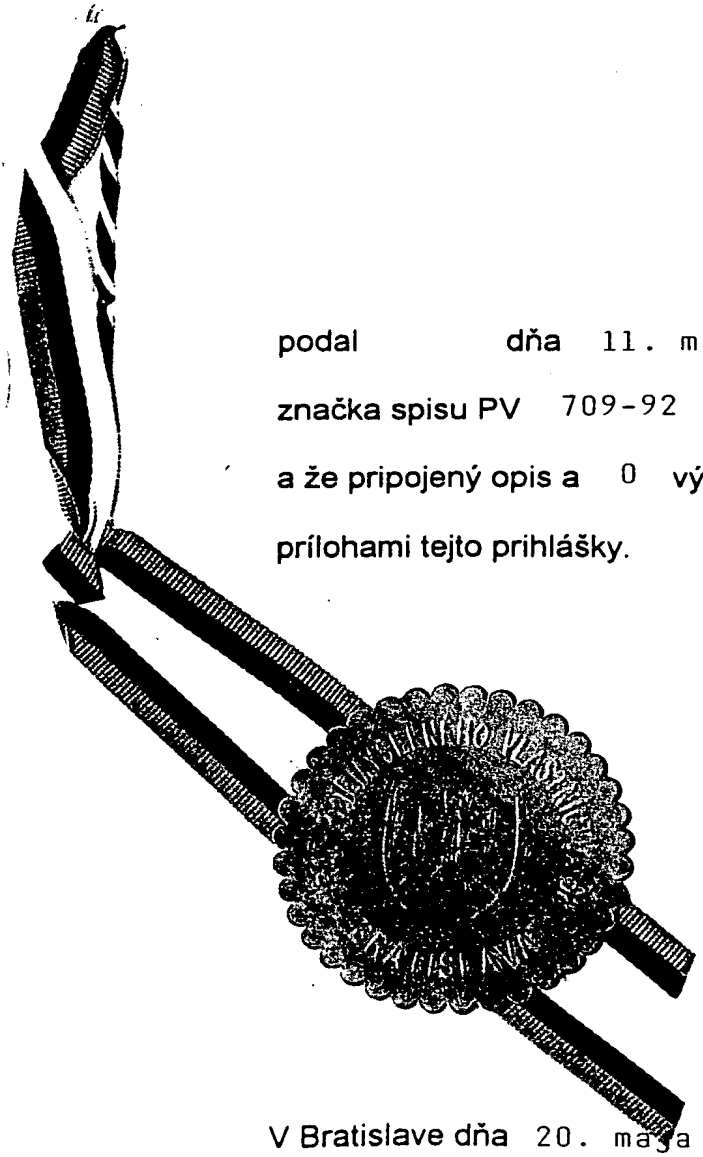
cc: Ellen Sampson
Leona Lauder ✓

Form BP4/9

SLOVENSKÁ REPUBLIKA

ÚRAD PRIEMYSELNÉHO VLASTNÍCTVA

potvrdzuje že, Virologický ústav SAV, Bratislava



podal dňa 11. marca 1992 prihlášku vynálezu

značka spisu PV 709-92

a že pripojený opis a 0 výkresov sa zhoduje úplne s pôvodne podanými prílohami tejto prihlášky.

Predseda

V Bratislave dňa 20. mája 1993

APPENDIX C

Názov vynálezu : Myší lymfocytárny hybridóm VÚ-M75

Pôvodcovia : ZÁVADA Ján, RNDr.DrSc., Bratislava
PASTOREKOVÁ Silvia, RNDr., Bratislava

Myší lymfocytárny hybridóm VÚ-M75

Oblasť techniky

Vynález sa týka myšieho lymfocytárneho hybridómu VÚ-M75, produkujúceho monoklonálne protilátky (podtrieda IgG2B) proti proteínu MN z ľudských nádorových buniek.

Doterajší stav techniky

Technika hybridómov, produkujúcich monoklonálne protilátky, je všeobecne známa a používaná (Köhler, G., Milstein, C.: Continuous cultures of fused cells secreting antibody of predefined specificity, Nature 256 /1975/). Monoklonálne protilátky sa používajú na identifikáciu a stanovenie rôznych antigénov. Monoklonálne protilátka resp. hybridóm produkujúco monoklonálnu protilátku proti proteínu MN z ľudských nádorových buniek doteraz nebola popísaná.

Podstata vynálezu

Podstatou vynálezu je hybridóm VÚ-M75, produkujúci monoklonálnu protilátku podtriedy IgG2B proti proteínu MN z ľudských nádorových buniek. Tento hybridóm je uložený v zbierke hybridómov Virologického ústavu SAV, Dúbravská cesta 9, 809 39 Bratislava, pod označením VÚ-M75.

Uvedený hybridóm bol získaný spôsobom známym z odbornej literatúry (Köhler, G., Milstein, C.: Continuous cultures of fused cells secreting antibody of predefined specificity, Nature 256 /1975/).

Monoklonálna protilátka, produkovaná hybridómom podľa vynálezu, slúži na identifikáciu proteínu MN v rôznych laboratórnych diagnostických testoch. Proteín MN /doteraz neznámy/ je produkovaný niektorými ľudskými nádorovými bunečnými líniami in vitro, bunkami niektorých zhubných nádorov in vivo (napr. karcinóm krčku maternice, ovaria, endometria) - - nenádorové bunky ho neprodukujú. Pozostáva z peptidických reťazcov o M_r = 48 000 - 58 000, ktoré navzájom tvoria oligoméry, viazané disulfidickými väzbami (ide asi o tri- tetraméry). Je glykozylovaný. V bunkách HeLa sú jeho peptidy vo dvoch veľkostiach - p 54/58 N.

Monoklonálne protilátky produkované hybridómom VÚ-M75 je možné využiť v diagnostike (imunofluorescenčná mikroskopia), ako komponenty v kvantitatívnom stanovení antigénu MN pomocou rádioimunoeseje, v imunoblotoch s proteínom MN priamo z ľudských nádorov, v imunoelektrónovej mikroskopii s koloidným zlatom na lokalizáciu antigénu MN v bunkách.

Príklad uskutočnenia vynálezu

Hybridóm VÚ-M75 sa získal klonovaním hybridných buniek získaných somatickou hybridizáciou myšej myelómovej bunkovej línie NS/0 a slezinových lymfoidných buniek syngénneho zvieraťa, imunizovaného prvýkrát intraperitoneálnou dávkou a druhýkrát intravenóznou dávkou (vyvolávacou) nádorovej bunečnej línie HeLa.

Bunky hybridómu rastú ako suspenzná kultúra buniek s morfológiou myších myelómových buniek. Základným kultivačným médiom je D-MEM s 10% fetálnym teľacím sérom a antibiotikom gentamycínom. Hybridóm je kultivovaný pri teplote 37 °C v 5% oxide uhličitom. Zo zmrazených ampulovaných vzoriek pôvodného hybridómu (v tekutom dusíku) je možné nové kultivovanie kultúry hybridómu a produkcie monoklonálnej protilátky, bez imunizácie a s pôvodnou špecificitou.

Priemyselné využitie

Monoklonálna protilátka produkovaná hybridómom podľa vynálezu môže sa využiť ako súčasť diagnostických súprav, môže sa po označení vhodným rádioizotopom použiť na lokalizáciu metastáz (pomocou scintigrafie), môže byť zložkou cytostatík pre liečbu. Okrem toho sa môže využiť v technológii génových manipulácií na izoláciu klonovaného génu MN, ktorý kóduje proteín MN.

P A T E N T O V É N Á R O K Y

Myší lymfocytárny hybridóm VÚ-M75, produkujúci monoklonálnu protilátku podtriedy IgG2B proti proteínu MN z ľudských nádorových buniek.

TRANSLATION

SLOVAK REPUBLIC

OFFICE OF INDUSTRIAL PROPERTY

certifies that **Institute of Virology of the Slovak Academy of Sciences, Bratislava**

filed on the 11th March 1992 a patent application

under the Serial No. PV 709-92

and that the attached specification and 0 drawings fully corresponds to the originally filed enclosures of this application.

Official seal:
OFFICE OF INDUSTRIAL
PROPERTY OF THE SR

President: Porubský s.m.
signature

Official stamp:
OFFICE OF INDUSTRIAL
PROPERTY

Bratislava, May 20, 1993

Title of the invention: Mouse lymphocytic hybridoma VÚ-M75

Authors: ZÁVADA Jan, RNDr.DrSc., Bratislava
PASTOREKOVÁ Silvia, RNDr., Bratislava

Mouse lymphocytic hybridoma VÚ-M75

Field of Technology

The invention concerns a mouse lymphocytic hybridoma VÚ-M75 producing the monoclonal antibody (isotype IgG2B), specific for the MN protein from human cancer cells.

Prior Art

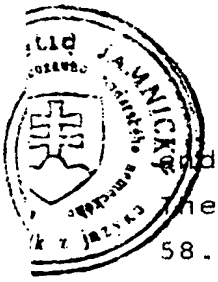
The technique of hybridomas producing monoclonal antibodies is generally known and used (Köhler, G., Milstein, C.: Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256 /1975/). Monoclonal antibodies are used for identification and determination of various antigens. Until now no monoclonal antobody or hybridoma, producing monoclonal antibody specific for MN protein from human cancer cells, has been described.

Summary of Invention

The subject of the present invention is hybridoma VÚ-M75, producing monoclonal antibody of IgG2B isotype, specific for MN protein from human cancer cells. This hybridoma is deposited in the Collection of hybridomas of the Institute of Virology, Slovak Academy of Sciences, Dúbravská cesta 9, 842 46 Bratislava, and it is designated as VÚ-M75.

The above-mentioned hybridoma has been constructed by the method known and described by Köhler, G., Milstein, C.: Continuous cultures of fused cells secreting antibody of predefined specificity. Nature 256 (1975).

Monoclonal antibody produced by the hybridoma according to the present invention serves for identification of MN protein in various laboratory diagnostic tests. The MN protein (until now unknown) is produced by some human cancer cell lines *in vitro*, and by the cells of some malignant tumors *in vivo* (e.g. carcinomas of uterine cervix, of ovary and of



(endometrium) - it is not produced by normal, non-cancer cells. The MN protein consists of peptidic chains of M_r = 48.000 to 58.000 which form the oligomers linked with disulphidic bonds (probably tri- or tetramers). The MN protein is glycosylated. In the HeLa cells its polypeptides are of two sizes - p54/58N.

Monoclonal antibodies produced by the hybridoma VÚ-M75 can be used in diagnostics (immunofluorescence microscopy), as components in quantitative radioimmunoassay for MN antigen, in immunoblots with MN protein extracted directly from human tumors, in immunoelectron microscopy using colloid gold for localization of MN antigen in the cells.

Example of Realization of Invention

Hybridoma VÚ-M75 has been obtained by cloning of hybrid cells produced by somatic cell hybridization of the mouse myeloma cell line NS/0 with spleen lymphoid cells of a syngeneic mouse, immunized for the first time with an intraperitoneal dose and for the second time with intravenous dose (challenging dose) of the cancer cell line HeLa.

Hybridoma cells grow as a suspension cell culture showing the morphology of mouse myeloma cells. As the basic cultivation medium is used the D-MEM containing 10% foetal calf serum and the antibiotic Gentamycin. The hybridoma is cultivated at 37 ^{0}C in 5% carbon dioxide (CO_2) atmosphere. Aliquots of the original hybridoma are stored in ampoules in liquid nitrogen; from these it can be recovered and further grown in culture where it continues producing monoclonal antibody without immunization and with the original specificity.

Industrial Exploitation

The monoclonal antibody produced by the hybridoma according to the present invention can by used as a component of diagnostic kits; after labelling with a suitable radioisotop. it can be used for localization of metastases

using scintigraphy); it can be used as a component of targeted cytostatics for therapy. In addition, it can be employd in technology of genetic manipulations for cloning of MN gene, which is coding for the MN protein.

C L A I M

Mouse lymphocytic hybridoma VÚ-M75, producing monoclonal antibody of IgG2B isotype which is specific for the MN protein from human cancer cells.

****

Číslo prekladu: 211/1993

Podpísaný JUDr.Aristid Jamnický, ako stály tlmočník jazyka anglického,českého,francúzskeho,nemeckého a maďarského,vymenovaný dekrétom Mestského súdu v Bratislave pod číslom Spr.3218/90 zo dňa 8. marca 1990,dosvedčujem,že tento anglický preklad doslovne sa zrovnáva so sem prišitou listinou vyhotovenou v jazyku slovenskom.Dôkazom čoho môj podpis a úradná pečiatka.Tlmočnícky úkon bol zapísaný do tlmočníckeho denníka. - - -

- - - - - - - - - - - - - - - - - - - -

Bratislava,dňa 9.júla 1993.

Stály tlmočník:

Number of the translation:211/1993

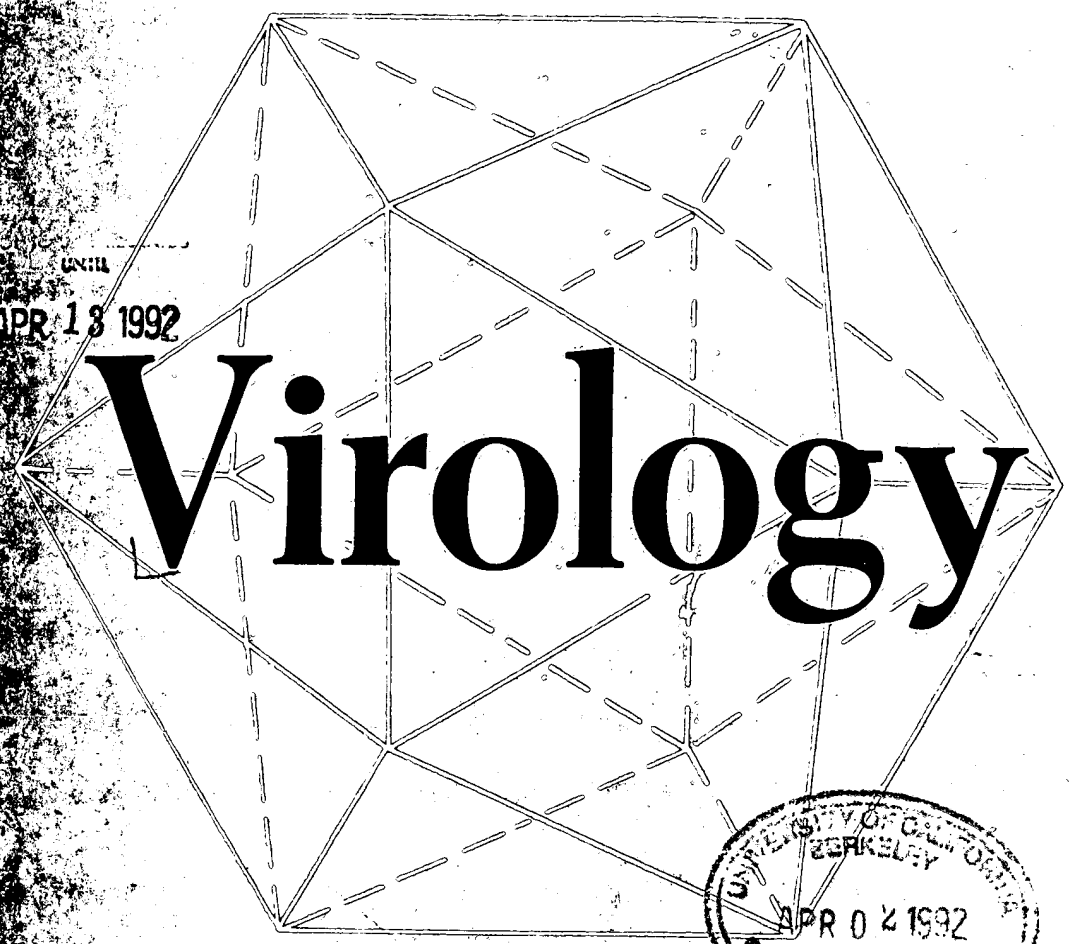
The undersigned JUDr.Aristid Jamnicky,as permanent Interpreter of the English,Czech,French, German and Hungarian languages, appointed by decree of the Municipal Court in Bratislava number Spr. 3218/90 the 8th of March 1990, do thereby certify,that this is a truth,true and faithful English translation of the hereto annexed document drawn up in the Slovak language.In faith and testimony thereof I have set my hand and Seal of Office.The translation was entered in the diary of translations. - - - -

Bratislava, the 9th of July 1993.

Permanent Interpreter :

THIS NUMBER COMPLETES VOLUME 187
VOLUME 187, NUMBER 2, APRIL 1992

ISSN 0042-6822



Virology

ACADEMIC PRESS, INC.
Harcourt Brace Jovanovich, Publishers
San Diego New York Boston
London Sydney Tokyo Toronto

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : **5,387,676**

DATED : **February 7, 1995**

INVENTOR(S) : **Jan Zavada et al.**

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Sheets 1 and 2 of the drawings consisting of Figures 1A and 1B should be deleted, and the attached Figures 1A and 1B should be inserted therefor.

Signed and Sealed this

Twenty-third Day of November, 1999

Attest:

Attesting Officer

Q. TODD DICKINSON

Acting Commissioner of Patents and Trademarks

APPENDIX E

```
  1  Gln Arg Leu Pro Arg Met Gln Glu Asp Ser Pro Leu Gly Gly Gly
  1  CAG AGG TTG CCC CGG ATG CAG GAG GAT TCC CCC TTG GGA GGA GGC

 16  Ser Ser Gly Glu Asp Asp Pro Leu Gly Glu Glu Asp Leu Pro Ser
 46  TCT TCT GGG GAA GAT GAC CCA CTG GGC GAG GAG GAT CTG CCC AGT

 31  Glu Glu Asp Ser Pro Arg Glu Glu Asp Pro Pro Gly Glu Glu Asp
 91  GAA GAG GAT TCA CCC AGA GAG GAG GAT CCA CCC GGA GAG GAG GAT

 46  Leu Pro Gly Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro Glu
136  CTA CCT GGA GAG GAG GAT CTA CCT GGA GAG GAG GAT CTA CCT GAA

 61  Val Lys Pro Lys Ser Glu Glu Glu Gly Ser Leu Lys Leu Glu Asp
181  GTT AAG CCT AAA TCA GAA GAA GAG GGC TCC CTG AAG TTA GAG GAT

 76  Leu Pro Thr Val Glu Ala Pro Gly Asp Pro Gln Glu Pro Gln Asn
226  CTA CCT ACT GTT GAG GCT CCT GGA GAT CCT CAA GAA CCC CAG AAT

 91  Asn Ala His Arg Asp Lys Glu Gly Asp Asp Gln Ser His Trp Arg
271  AAT GCC CAC AGG GAC AAA GAA GGG GAT GAC CAG AGT CAT TGG CGC

106  Tyr Gly Gly Asp Pro Pro Trp Pro Arg Val Ser Pro Ala Cys Ala
316  TAT GGA GGC GAC CCG CCC TGG CCC CGG GTG TCC CCA GCC TGC GCG

121  Gly Arg Phe Gln Ser Pro Val Asp Ile Arg Pro Gln Leu Ala Ala
361  GGC CGC TTC CAG TCC CCG GTG GAT ATC CGC CCC CAG CTC GCC GCC

136  Phe Cys Pro Ala Leu Arg Pro Leu Glu Leu Leu Gly Phe Gln Leu
406  TTC TGC CCG GCC CTG CGC CCC CTG GAA CTC CTG GGC TTC CAG CTC

151  Pro Pro Leu Pro Glu Leu Arg Leu Arg Asn Asn Gly His Ser Val
451  CCG CCG CTC CCA GAA CTG CGC CTG CGC AAC AAT GGC CAC AGT GTG

166  Gln Leu Thr Leu Pro Pro Gly Leu Glu Met Ala Leu Gly Pro Gly
496  CAA CTG ACC CTG CCT CCT GGG CTA GAG ATG GCT CTG GGT CCC GGG

191  Arg Glu Tyr Arg Ala Leu Gln Leu His Leu His Trp Gly Ala Ala
541  CGG GAG TAC CGG GCT CTG CAG CTG CAT CTG CAC TGG GGG GCT GCA

196  Gly Arg Pro Gly Ser Glu His Thr Val Glu Gly His Arg Phe Pro
586  GGT CGT CCG GGC TCG GAG CAC ACT GTG GAA GGC CAC CGT TTC CCT

211  Ala Glu Ile His Val Val His Leu Ser Thr Ala Phe Ala Arg Val
631  GCC GAG ATC CAC GTG GTT CAC CTC AGC ACC GCC TTT GCC AGA GTT
```

FIG. 1A

```
226   Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu Ala Val Leu Ala Ala
676   GAC GAG GCC TTG GGG CGC CCG GGA GGC CTG GCC GTG TTG GCC GCC

241   Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala Tyr Glu Gln Leu
721   TTT CTG GAG GAG GGC CCG GAA GAA AAC AGT GCC TAT GAG CAG TTG

256   Leu Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser Glu Thr Gln
766   CTG TCT CGC TTG GAA GAA ATC GCT GAG GAA GGC TCA GAG ACT CAG

271   Val Pro Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp Phe Ser
811   GTC CCA GGA CTG GAC ATA TCT GCA CTC CTG CCC TCT GAC TTC AGC

286   Arg Tyr Phe Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys Ala
856   CGC TAC TTC CAA TAT GAG GGG TCT CTG ACT ACA CCG CCC TGT GCC

301   Gln Gly Val Ile Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser
901   CAG GGT GTC ATC TGG ACT GTG TTT AAC CAG ACA GTG ATG CTG AGT

316   Ala Lys Gln Leu His Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly
946   GCT AAG CAG CTC CAC ACC CTC TCT GAC ACC CTG TGG GGA CCT GGT

331   Asp Ser Arg Leu Gln Leu Asn Phe Arg Ala Thr Gln Pro Leu Asn
991   GAC TCT CGG CTA CAG CTG AAC TTC CGA GCG ACG CAG CCT TTG AAT

346   Gly Arg Val Ile Glu Ala Ser Phe Pro Ala Gly Val Asp Ser Ser
1046  GGG CGA GTG ATT GAG GCC TCC TTC CCT GCT GGA GTG GAC AGC AGT

361   Pro Arg Ala Ala Glu Pro Val Gln Leu Asn Ser Cys Leu Ala Ala
1081  CCT CGG GCT GCT GAG CCA GTC CAG CTG AAT TCC TGC CTG GCT GCT

376   Gly Asp Ile Leu Ala Leu Val Phe Gly Leu Leu Phe Ala Val Thr
1126  GGT GAC ATC CTA GCC CTG GTT TTT GGC CTC CTT TTT GCT GTC ACC

391   Ser Val Ala Phe Leu Val Gln Met Arg Arg Gln His Arg Arg Gly
1171  AGC GTC GCG TTC CTT GTG CAG ATG AGA AGG CAG CAC AGA AGG GGA

406   Thr Lys Gly Gly Val Ser Tyr Arg Pro Ala Glu Val Ala Glu Thr
1216  ACC AAA GGG GGT GTG AGC TAC CGC CCA GCA GAG GTA GCC GAG ACT

421   Gly Ala
1261  GGA GCC TAG AGG CTG GAT CTT GGA GAA TGT GAG AAG CCA GCC AGA

1306  GGC ATC TGA GGG GGA GCC GGT AAC TGT CCT GTC CTG CTC ATT ATG

1351  CCA CTT CCT TTT AAC TGC CAA GAA ATT TTT TAA AAT AAA TAT TTA

1396  TAA T
```

FIG. 1B

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 37, line 16, through column 44, line 37, "SEQUENCE LISTING" should read

--

SEQUENCE LISTING

<110> Zavada, Jan
Pastorekova, Silvia
Pastorek, Jaromir

<120> MN Gene and Protein

<130> D-0021

<140> 07/964,589
<141> 1992-10-21

<160> 4

<170> PatentIn Ver. 2.0

<210> 1
<211> 1399
<212> DNA
<213> Human

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

<220>
<221> CDS
<222> (1)..(1266)

<400> 1

```
cag agg ttg ccc cgg atg cag gag gat tcc ccc ttg gga gga ggc tct   48
Gln Arg Leu Pro Arg Met Gln Glu Asp Ser Pro Leu Gly Gly Gly Ser
  1               5                  10                  15

tct ggg gaa gat gac cca ctg ggc gag gag gat ctg ccc agt gaa gag   96
Ser Gly Glu Asp Asp Pro Leu Gly Glu Glu Asp Leu Pro Ser Glu Glu
             20                  25                  30

gat tca ccc aga gag gag gat cca ccc gga gag gag gat cta cct gga  144
Asp Ser Pro Arg Glu Glu Asp Pro Pro Gly Glu Glu Asp Leu Pro Gly
         35                  40                  45

gag gag gat cta cct gga gag gag gat cta cct gaa gtt aag cct aaa  192
Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro Glu Val Lys Pro Lys
     50                  55                  60

tca gaa gaa gag ggc tcc ctg aag tta gag gat cta cct act gtt gag  240
Ser Glu Glu Glu Gly Ser Leu Lys Leu Glu Asp Leu Pro Thr Val Glu
 65                  70                  75                  80
```

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
gct cct gga gat cct caa gaa ccc cag aat aat gcc cac agg gac aaa   288
Ala Pro Gly Asp Pro Gln Glu Pro Gln Asn Asn Ala His Arg Asp Lys
                 85                  90                  95

gaa ggg gat gac cag agt cat tgg cgc tat gga ggc gac ccg ccc tgg   336
Glu Gly Asp Asp Gln Ser His Trp Arg Tyr Gly Gly Asp Pro Pro Trp
            100                 105                 110

ccc cgg gtg tcc cca gcc tgc gcg ggc cgc ttc cag tcc ccg gtg gat   384
Pro Arg Val Ser Pro Ala Cys Ala Gly Arg Phe Gln Ser Pro Val Asp
        115                 120                 125

atc cgc ccc cag ctc gcc gcc ttc tgc ccg gcc ctg cgc ccc ctg gaa   432
Ile Arg Pro Gln Leu Ala Ala Phe Cys Pro Ala Leu Arg Pro Leu Glu
    130                 135                 140

ctc ctg ggc ttc cag ctc ccg ccg ctc cca gaa ctg cgc ctg cgc aac   480
Leu Leu Gly Phe Gln Leu Pro Pro Leu Pro Glu Leu Arg Leu Arg Asn
145                 150                 155                 160

aat ggc cac agt gtg caa ctg acc ctg cct cct ggg cta gag atg gct   528
Asn Gly His Ser Val Gln Leu Thr Leu Pro Pro Gly Leu Glu Met Ala
                165                 170                 175
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
ctg ggt ccc ggg cgg gag tac cgg gct ctg cag ctg cat ctg cac tgg   576
Leu Gly Pro Gly Arg Glu Tyr Arg Ala Leu Gln Leu His Leu His Trp
            180                 185                 190

ggg gct gca ggt cgt ccg ggc tcg gag cac act gtg gaa ggc cac cgt   624
Gly Ala Ala Gly Arg Pro Gly Ser Glu His Thr Val Glu Gly His Arg
        195                 200                 205

ttc cct gcc gag atc cac gtg gtt cac ctc agc acc gcc ttt gcc aga   672
Phe Pro Ala Glu Ile His Val Val His Leu Ser Thr Ala Phe Ala Arg
    210                 215                 220

gtt gac gag gcc ttg ggg cgc ccg gga ggc ctg gcc gtg ttg gcc gcc   720
Val Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu Ala Val Leu Ala Ala
225                 230                 235                 240

ttt ctg gag gag ggc ccg gaa gaa aac agt gcc tat gag cag ttg ctg   768
Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala Tyr Glu Gln Leu Leu
                245                 250                 255

tct cgc ttg gaa gaa atc gct gag gaa ggc tca gag act cag gtc cca   816
Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser Glu Thr Gln Val Pro
            260                 265                 270
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
gga ctg gac ata tct gca ctc ctg ccc tct gac ttc agc cgc tac ttc   864
Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp Phe Ser Arg Tyr Phe
        275                 280                 285

caa tat gag ggg tct ctg act aca ccg ccc tgt gcc cag ggt gtc atc   912
Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys Ala Gln Gly Val Ile
    290                 295                 300

tgg act gtg ttt aac cag aca gtg atg ctg agt gct aag cag ctc cac   960
Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser Ala Lys Gln Leu His
305                 310                 315                 320

acc ctc tct gac acc ctg tgg gga cct ggt gac tct cgg cta cag ctg  1008
Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly Asp Ser Arg Leu Gln Leu
                325                 330                 335

aac ttc cga gcg acg cag cct ttg aat ggg cga gtg att gag gcc tcc  1056
Asn Phe Arg Ala Thr Gln Pro Leu Asn Gly Arg Val Ile Glu Ala Ser
            340                 345                 350

ttc cct gct gga gtg gac agc agt cct cgg gct gct gag cca gtc cag  1104
Phe Pro Ala Gly Val Asp Ser Ser Pro Arg Ala Ala Glu Pro Val Gln
        355                 360                 365
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
ctg aat tcc tgc ctg gct gct ggt gac atc cta gcc ctg gtt ttt ggc   1152
Leu Asn Ser Cys Leu Ala Ala Gly Asp Ile Leu Ala Leu Val Phe Gly
    370                 375                 380

ctc ctt ttt gct gtc acc agc gtc gcg ttc ctt gtg cag atg aga agg   1200
Leu Leu Phe Ala Val Thr Ser Val Ala Phe Leu Val Gln Met Arg Arg
385                 390                 395                 400

cag cac aga agg gga acc aaa ggg ggt gtg agc tac cgc cca gca gag   1248
Gln His Arg Arg Gly Thr Lys Gly Gly Val Ser Tyr Arg Pro Ala Glu
                405                 410                 415

gta gcc gag act gga gcc tagaggctgg atcttggaga atgtgagaag         1296
Val Ala Glu Thr Gly Ala
            420

ccagccagag gcatctgagg gggagccggt aactgtcctg tcctgctcat tatgccactt 1356

ccttttaact gccaagaaat tttttaaaat aaatatttat aat                   1399


<210> 2
<211> 422
<212> PRT
<213> Human
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

<400> 2

```
Gln Arg Leu Pro Arg Met Gln Glu Asp Ser Pro Leu Gly Gly Gly Ser
 1               5                  10                  15

Ser Gly Glu Asp Asp Pro Leu Gly Glu Glu Asp Leu Pro Ser Glu Glu
            20                  25                  30

Asp Ser Pro Arg Glu Glu Asp Pro Pro Gly Glu Glu Asp Leu Pro Gly
        35                  40                  45

Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro Glu Val Lys Pro Lys
    50                  55                  60

Ser Glu Glu Glu Gly Ser Leu Lys Leu Glu Asp Leu Pro Thr Val Glu
65                  70                  75                  80

Ala Pro Gly Asp Pro Gln Glu Pro Gln Asn Asn Ala His Arg Asp Lys
                85                  90                  95

Glu Gly Asp Asp Gln Ser His Trp Arg Tyr Gly Gly Asp Pro Pro Trp
            100                 105                 110

Pro Arg Val Ser Pro Ala Cys Ala Gly Arg Phe Gln Ser Pro Val Asp
        115                 120                 125
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
Ile Arg Pro Gln Leu Ala Ala Phe Cys Pro Ala Leu Arg Pro Leu Glu
    130                 135                 140

Leu Leu Gly Phe Gln Leu Pro Pro Leu Pro Glu Leu Arg Leu Arg Asn
145                 150                 155                 160

Asn Gly His Ser Val Gln Leu Thr Leu Pro Pro Gly Leu Glu Met Ala
                165                 170                 175

Leu Gly Pro Gly Arg Glu Tyr Arg Ala Leu Gln Leu His Leu His Trp
            180                 185                 190

Gly Ala Ala Gly Arg Pro Gly Ser Glu His Thr Val Glu Gly His Arg
        195                 200                 205

Phe Pro Ala Glu Ile His Val Val His Leu Ser Thr Ala Phe Ala Arg
    210                 215                 220

Val Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu Ala Val Leu Ala Ala
225                 230                 235                 240

Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala Tyr Glu Gln Leu Leu
                245                 250                 255
```

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

```
Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser Glu Thr Gln Val Pro
            260                 265                 270

Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp Phe Ser Arg Tyr Phe
        275                 280                 285

Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys Ala Gln Gly Val Ile
    290                 295                 300

Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser Ala Lys Gln Leu His
305                 310                 315                 320

Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly Asp Ser Arg Leu Gln Leu
                325                 330                 335

Asn Phe Arg Ala Thr Gln Pro Leu Asn Gly Arg Val Ile Glu Ala Ser
            340                 345                 350

Phe Pro Ala Gly Val Asp Ser Ser Pro Arg Ala Ala Glu Pro Val Gln
        355                 360                 365

Leu Asn Ser Cys Leu Ala Ala Gly Asp Ile Leu Ala Leu Val Phe Gly
    370                 375                 380

Leu Leu Phe Ala Val Thr Ser Val Ala Phe Leu Val Gln Met Arg Arg
385                 390                 395                 400
```

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,387,676

DATED : February 7, 1995

INVENTOR(S) : Jan Zavada et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Gln His Arg Arg Gly Thr Lys Gly Gly Val Ser Tyr Arg Pro Ala Glu
405 410 415

Val Ala Glu Thr Gly Ala
420

<210> 3
<211> 29
<212> DNA
<213> HUMAN

<400> 3
cgcccagtgg gtcatcttcc ccagaagag 29

<210> 4
<211> 19
<212> DNA
<213> HUMAN

<400> 4
ggaatcctcc tgcatccgg 19 --